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DOCKET NO.: **19603/606 (CRF D-1657B)**
EXPRESS MAIL NO.: **EL434571524US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

UTILITY PATENT APPLICATION TRANSMITTAL FORM
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ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231
BOX: PATENT APPLICATION

SIR:

Transmitted herewith for filing is the patent application (including Specification, Claims, Sequence Listing, and Abstract, (94 pages)) of:

Inventor(s): **David M. Soderlund, Douglas C. Knipple, and Patricia J. Ingles**

For : **INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES**

***If a CONTINUING APPLICATION, please mark where appropriate and supply the requisite information below and in a preliminary amendment:*

[ ] *continuation* [X] *divisional* [ ] *Continuation-In-Part (CIP) of prior application Serial No. 08/772,512*

Prior application information: Examiner : J. LeGuyader
Art Unit : 1635

Enclosed are:

[X] Submission of Formal Drawings with 7 sheets of formal drawings.

[ ] **Signed** Combined Declaration and Power of Attorney (_____ pages).

[X] **Copy** of **signed** Combined Declaration and Power of Attorney (2 pages) from a prior application (1.63(d) (for continuation/divisional).

[ ] **Signed** statement deleting inventor(s) named in prior application (_____ pages) (1.63(d)(2) and 1.33(b)).

[X] **Incorporation By Reference**: The entire disclosure of the prior application, from which a **copy** of the oath or declaration is supplied herewith, is considered as being part of the disclosure of the enclosed application and is hereby incorporated by reference therein.

[ ] Assignment (_____ pages) of the invention to ________________________________.

[ ] Assignment Transmittal Letter.

[ ] Certified copy of a foreign priority document.

[ ] Associate power of attorney.

[X] Verified statement to establish small entity status (2 pages) (copy filed in prior application).

[X] Preliminary Amendment (3 pages).

[X] Information Disclosure Statement, form PTO-1449 (3 pages) and no references.

[ ] **UNSIGNED** Combined Declaration and Power of Attorney (_____ pages).

[X] Statement in Accordance with 37 CFR § 1.821(f) and computer readable 3.5" Diskette.

[X] A self-addressed, prepaid postcard acknowledging receipt.

[ ] Other:

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[X] Address all future communications to:

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EXPRESS MAIL CERTIFICATE

DOCKET NO.: **19603/606 (CRF D-1657B)**

APPLICANTS: **David M. Soderlund, Douglas C. Knipple, and Patricia J. Ingles**

TITLE: **INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES**

Certificate is attached to the **Patent Application including specification, claims, sequence listing and abstract (94 pages), the Unsigned Combined Declaration and Power of Attorney (2 pages), and drawings (6 pages)** as filed in the prior application of the above-named application.

EXPRESS MAIL NUMBER: **EL434571524US**

DATE OF DEPOSIT: **October 28, 1999**

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Ruth R. Smith
(Signature of person mailing paper or fee)

PATENT

Attorney's Docket No. 19603/601 (CRF D-1657)

Applicant or Patentee: David M. Soderlund, Douglas C. Knipple, Patricia J. Ingles

Serial or Patent No.: 08/ 772,512

Filed or Issued: December 24, 1996

For: INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9 (F) AND 1.27(d))--NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION CORNELL RESEARCH FOUNDATION, INC.

ADDRESS OF ORGANIZATION 20 Thornwood Drive, Suite 105
Ithaca, New York 14850

TYPE OF ORGANIZATION

*☒ UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION

☐ TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501 (a) and 501 (c)(3))

☐ NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE ____________________)
(CITATION OF STATUTE ____________________)

☐ WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501 (a) and (501 (c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA

☐ WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE ____________________)
(CITATION OF STATUTE ____________________)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES

by inventor(s) David M. Soderlund, Douglas C. Knipple, Patricia J. Ingles

described in

☐ the specification filed herewith.

☒ application serial no. 08/ 772,512, filed December 24, 1996.

☐ patent no. ____________, issued ____________.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

**NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).*

NAME ______________________________
ADDRESS ______________________________

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME ______________________________
ADDRESS ______________________________

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any charge in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING H. Walter Haeussler
TITLE IN ORGANIZATION President
ADDRESS OF PERSON SIGNING 20 Thornwood Drive, Suite 105
Ithaca, New York 14850

SIGNATURE H. Walter Haeussler Date March 14, 1997

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PATENT
Docket No.: **19603/606 (CRF D-1657B)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	David M. Soderlund, Douglas C. Knipple, and Patricia J. Ingles	)	Examiner: To Be Assigned
Serial No.	:	To Be Assigned (Division of Serial No. 08/772,512, filed December 24, 1996)	)	Art Unit: To Be Assigned
Filed	:	Herewith	)	
For	:	INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231
Box: Patent Application

Dear Sir:

Please amend the above-identified patent application as follows:

In the Specification:

On page 1, line 8, after "This application is a", insert --divisional application of Serial No. 08/772,512, filed on December 24, 1996, which is a--.

On page 6, line 29, replace "________" with --97831--.

On page 6, line 32, replace "________" with -- 97832--.

On page 8, line 23, replace "________" with --97831--.

On page 8, line 24, replace "________" with --97832--.

On page 8, line 25, replace "December ___" with --December 20--.

On page 28, line 1, replace "________" with --97831--.

On page 28, line 4, replace "________" with --97832--.

In the Claims:

Please cancel claims 1-40 and 53-77, without prejudice.

Please amend claim 41, as follows:

41. (Amended) A method of screening a chemical agent for the ability of the chemical agent to modify sodium channel function, said method comprising:

introducing an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of *Musca domestica*, wherein said nucleic acid molecule hybridizes to a nucleic acid molecule, having a nucleotide sequence according to bases 1 to 1011 or 1321 to 5030 of SEQ. ID. No. 1 or 3 at 42°, with 5 x SSPC and 50% formamide with washing at 65° C with 0.5 x SSPC [the nucleic acid molecule of claim 1] into a host cell;

expressing said voltage-sensitive sodium channel encoded by said nucleic acid molecule in the host cell so as to result in the functional expression of a voltage-sensitive sodium channel in the host cell;

exposing the host cell to a chemical agent; and

evaluating the exposed host cell to determine if the chemical agent modifies the function of the voltage-sensitive sodium channel.

Please add new claims 78-83, as follows:

78. (New) The method according to claim 41, wherein said voltage-sensitive sodium channel confers susceptibility to an insecticide in *Musca domestica*.

79. (New) The method according to claim 78, wherein said nucleic acid molecule has a nucleotide sequence as shown in SEQ ID NO:1.

80. (New) The method according to claim 78, wherein said nucleic acid molecule encodes an amino acid sequence as shown in SEQ ID NO:3.

81. (New) The method according to claim 41, wherein said voltage-sensitive sodium channel confers resistance to an insecticide in *Musca domestica*.

82. (New) The method according to claim 81, wherein said nucleic acid molecule has a nucleotide sequence as shown in SEQ ID NO:2.

83. (New) The method according to claim 41, wherein said nucleic acid molecule encodes an amino acid sequence as shown in SEQ ID NO:4.

REMARKS

In view of the above amendments, it is submitted that this case is in condition for allowance, and such allowance is earnestly solicited.

Respectfully submitted,

Date: 10/28/99

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INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES

The subject matter of this application was made with support from the United States Government under USDA Grant No. 94-37302-0408.

This application is a continuation-in-part of U.S. Serial No. 08/608,618, filed March 1, 1996, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates generally to insect sodium channel proteins, and more particularly to insecticide-susceptible and insecticide-resistant voltage-sensitive sodium channels of the house fly *Musca domestica*.

BACKGROUND OF THE INVENTION

Throughout this application various publications are referenced, many in parenthesis. Full citations for these publications are provided at the end of the Detailed Description. The disclosures of these publications in their entireties are hereby incorporated by reference in this application.

Cell membranes must allow passage of various polar molecules, including ions, sugars, amino acids, and nucleotides. Special membrane proteins are responsible for transferring such molecules across cell membranes. These proteins, referred to as membrane transport proteins, occur in many forms and in all types of biological membranes. Each protein is specific in that it transports a particular class of molecules (such as ions, sugars, or amino acids) and often only certain molecular species of the class. All membrane transport proteins that have been studied in detail have been found to be multipass transmembrane proteins. By forming a continuous

protein pathway across the membrane, these proteins enable the specific molecules to cross the membrane without coming into direct contact with the hydrophobic interior of the lipid bilayer of the plasma membrane.

There are two major classes of membrane transport proteins: carrier proteins and channel proteins. Carrier proteins bind the specific molecule to be transported and undergo a series of conformational changes in order to transfer the bound molecule across the membrane. Channel proteins, on the other hand, need not bind the molecule. Instead, they form hydrophilic pores that extend across the lipid bilayer; when these pores are open, they allow specific molecules (usually inorganic ions of appropriate size and charge) to pass through them and thereby cross the membrane. Transport through channel proteins occurs at a much faster rate than transport mediated by carrier proteins.

Channel proteins which are concerned specifically with inorganic ion transport are referred to as ion channels, and include ion channels for sodium, potassium, calcium, and chloride ions. Ion channels which open in response to a change in the voltage across the membrane are referred to as voltage-sensitive ion channels.

The sodium channel is one of the most thoroughly characterized of the voltage-sensitive channels (see Fig. 1 for a model of a voltage-sensitive sodium channel). In vertebrates, sodium channels in the brain, muscle, and other tissues are large membrane glycoprotein complexes composed of an alpha subunit (230-270 kDa) and 1-2 tightly associated smaller (33-38 kDa) beta subunits (reviewed by Catterall 1992). The large alpha subunit forms the ion permeable pore while the smaller subunits play key roles in the regulation of channel function (Isom et al. 1992; reviewed by Isom et al. 1994). The alpha

subunit is common to purified channel preparations from *Electrophorus electricus* (electric eel) electric organ (Noda et al. 1984), rat brain (Noda et al. 1986), rat skeletal muscle (Barchi 1988) and chick heart muscle (Catterall 1986). Other studies have revealed the existence of multiple closely related isoforms of the sodium channel found in different animal species, in different tissues within the same species, and even in the same tissue (Catterall et al. 1981; Frelin et al. 1984; Rogart 1986; Moczydlowski et al. 1986).

The structure of invertebrate sodium channels is not as well defined. Gene cloning studies have established the existence of alpha subunits of structure similar to those described for vertebrates (Loughney et al. 1989; Ramaswami and Tanouye 1989; Okamoto et al. 1987). Analysis of the *para* behavioral mutant (paralytic; Suzuki et al. 1971) of *Drosophila melanogaster* revealed that the *para* gene encodes a *Drosophila* sodium channel alpha subunit (Loughney et al. 1989). The entire *para* cDNA sequence was determined (Loughney et al. 1989; Thackeray and Ganetzky 1994).

The *kdr* mutant of the house fly *Musca domestica* has also been studied. The *kdr* insecticide resistance trait of the house fly confers reduced neuronal sensitivity to the rapid paralytic and lethal actions of DDT and pyrethroid insecticides (Soderlund and Bloomquist 1990). Because these insecticides are known to modify neuronal excitability by altering the inactivation kinetics of voltage-sensitive sodium channels (Soderlund and Bloomquist 1989; Bloomquist 1993), efforts to identify the molecular basis of *kdr* resistance have focused on the pharmacology and structure of this target.

Recently, tight genetic linkage between the *kdr* trait and a restriction fragment length polymorphism located within a segment of the house fly homolog of the

para gene of *Drosophila melanogaster* was demonstrated (Knipple et al. 1994). Similar linkage studies have also documented tight linkage of the *super-kdr* resistance trait of the house fly (Williamson et al. 1993) to molecular markers lying within the *para*-homologous voltage-sensitive sodium channel gene.

Elucidation of the structure of the house fly sodium channel gene will enable the screening of potential insecticidal agents which act upon the sodium channel.

A need continues to exist, therefore, for the determination of the primary structure of the house fly sodium channel, i.e. the nucleotide and amino acid sequences of the channel.

SUMMARY OF INVENTION

To this end, the subject invention provides the 6318 nucleotide coding sequence (SEQ ID NO:1) of the voltage-sensitive sodium channel gene from insecticide-susceptible (NAIDM strain) house flies (*Musca domestica*), determined by automated direct DNA sequencing of PCR fragments obtained by amplification on first strand cDNA from adult heads. The deduced 2105-residue amino acid sequence (SEQ ID NO:3) exhibits overall structure and organization typical of sodium channel alpha subunit genes and is 90.0% identical to that of the *D. melanogaster para* gene product. There is no evidence for the existence of multiple splice variants among voltage-sensitive sodium channel cDNAs obtained from adult house fly head preparations. Comparison of the coding sequence of the voltage-sensitive sodium channel gene of the *kdr* insecticide-resistant house fly strain (538ge strain) to that of the NAIDM strain reveals 12 amino acid differences in the 538ge strain. The amino acid sequence (SEQ ID NO:4) of the *Kdr* strain is only 2104 residues in length, as a result of five (5) amino acid substitutions, four (4)

amino acid deletions, and three (3) amino acid insertions as compared to the 2105-residue amino acid sequence (SEQ ID NO:3) of the NAIDM strain. The nucleotide sequence (SEQ ID NO:2) of the *Kdr* strain is therefore 6315 nucleotides in length, which is three nucleotides shorter than the nucleotide sequence (SEQ ID NO:1) of the NAIDM strain.

More particularly, the subject invention provides an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of *Musca domestica*, wherein the voltage-sensitive sodium channel is capable of conferring sensitivity or resistance to an insecticide in *Musca domestica*. In one embodiment, the nucleic acid molecule confers insecticide susceptibility to the house fly, and in another embodiment the nucleic acid molecule confers insecticide resistance to the house fly. The nucleic acid molecule conferring insecticide resistance is preferably a mutated form of the nucleic acid molecule encoding the insecticide susceptible channel. The invention also provides an antisense nucleic acid molecule complementary to mRNA encoding the voltage-sensitive sodium channel of *Musca domestica*.

The isolated nucleic acid molecules of the invention can be inserted into suitable expression vectors and/or host cells. Expression of the nucleic acid molecules encoding the sodium channels results in production of functional sodium channels in a host cell. Expression of the antisense nucleic acid molecules or fragments thereof in a host cell results in decreased expression of the functional sodium channels.

The invention further provides a ribozyme having a recognition sequence complementary to a portion of mRNA encoding a voltage-sensitive sodium channel of *Musca domestica*. The ribozyme can be introduced into a

cell to also achieve decreased expression of sodium channels in the cell.

The invention further provides a method of screening a chemical agent for the ability of the chemical agent to modify sodium channel function, and a method of obtaining DNA encoding a voltage-sensitive sodium channel of *Musca domestica*.

Further provided is an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of an insect, wherein the nucleic acid molecule encodes a first amino acid sequence having at least 95% amino acid identity to a second amino acid sequence. The second amino acid sequence is, in two preferred embodiments, SEQ ID NO:3 or SEQ ID NO:4.

The invention also provides an isolated voltage-sensitive sodium channel of *Musca domestica*, and antibodies or antibody fragments specific for the sodium channel. The antibodies or antibody fragments can be used to detect the presence of the sodium channel in samples.

Further provided is an isolated voltage-sensitive sodium channel of *Musca domestica*, wherein the voltage-sensitive sodium channel is comprised of a protein having a first amino acid sequence with at least 95% amino acid identity to a second amino acid sequence. In two preferred embodiments, the second amino acid sequence is SEQ ID NO:3 or SEQ ID NO:4.

Also provided by the subject invention is a plasmid designated pPJI1 and deposited with the ATCC under Accession No._______, as well as a KpnI/AatII restriction fragment of about 3620 bp of the plasmid designated pPJI1. Further provided is a plasmid designated pPJI2 and deposited with the ATCC under Accession No. ______, as well as an AatII/SphII restriction fragment of about 2700 bp of the plasmid designated pPJI2. When the above two restriction fragments are ligated together at their AatII

sites, the resulting nucleic acid molecule encodes a voltage-sensitive sodium channel which confers susceptibility to an insecticide in *Musca domestica*. This resulting nucleic acid molecule is also provided by the subject invention.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features and advantages of this invention will be evident from the following detailed description of preferred embodiments when read in conjunction with the accompanying drawings in which:

Fig. 1 is a model of a voltage sensitive sodium channel from mammalian brain in the plasma membrane. The alpha and $beta_1$ subunits interact noncovalently; the alpha and $beta_2$ subunits are linked by disulfide bonds. The branched structures at the outer surface of the channel represent oligosaccharides;

Fig. 2 is a diagram of the structural organization of the voltage-sensitive sodium channel coding sequence of *Musca domestica* (*Vssc1*) showing repeated homology domains I-IV and putative transmembrane helices (rectangles). Shown below the structural organization are the relative length and location of the previously-described 309-nucleotide exon of *Vssc1* (Knipple *et al*. 1994) (exon) and seven overlapping PCR-amplified cDNA fragments (A-G) employed as templates for DNA sequencing;

Fig. 3 shows the alignment of the predicted amino acid sequences of $Vssc1^{NAIDM}$ (NAIDM) and $Vssc1^{538ge}$ (538ge) with that of the $a^+b^-c^-d^+e^-f^-h^-i^+$ splice variant of the *D. melanogaster para* sequence (para) obtained using the DNASTAR computer program (Clustal method). Residues that are identical to the NAIDM sequence in both 538ge and para are indicated as dashes (-) in the latter two sequences; gaps introduced to obtain optimal alignment are

indicated as periods (.). The locations of 24 putative helical transmembrane domains (e.g., IS1, IS2, etc.) and four putative pore-forming domains (e.g., IP, IIP) are marked by solid bars above the NAIDM sequence. Also marked above the NAIDM sequence are possible sites for *N*-linked glycosylation (#), cAMP-dependent protein kinase phosphorylation (*), and protein kinase C phosphorylation (●); and

Fig. 4 is a diagram of the *Vssc1* gene product showing the locations of 12 amino acid differences identified in the *Vssc1*^{538ge} sequence, including 5 amino acid substitutions, 4 amino acid deletions, and 3 amino acid insertions in the Vssc1^{538ge} sequence (R) as compared to the Vssc1^{NAIDM} sequence (S).

DETAILED DESCRIPTION

The plasmids designated pPJI1 and pPJI2 have each been deposited pursuant to, and in satisfaction of, the requirements of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland, 20852 under ATCC Accession No. ________ (pPJI1) and ATCC Accession No.________ (pPJI2). Both deposits were made on December ___, 1996.

As used herein, the term "isolated" when used in conjunction with a nucleic acid molecule refers to: 1) a nucleic acid molecule which has been separated from an organism in a substantially purified form (i.e. substantially free of other substances originating from that organism), or 2) a nucleic acid molecule having the same nucleotide sequence but not necessarily separated from the organism (i.e. synthesized nucleic acid molecules). The term "isolated" when used in conjunction with a channel refers to a channel encoded by such an

"isolated" nucleic acid molecule, generally expressed in a membrane, such as a plasma membrane within a cell or a synthetic lipid bilayer membrane. The expressed "isolated" channel has the pharmacological properties of a functional sodium channel.

As further used herein, the terms "corresponding to" or "having" or "as shown in" when used in conjunction with a SEQ ID NO for a nucleotide sequence refer to a nucleotide sequence which is substantially the same nucleotide sequence, or derivatives or equivalents thereof (such as deletion and hybrid variants thereof, splice variants thereof, etc.). Nucleotide additions, deletions, and/or substitutions, such as those which do not affect the translation of the DNA molecule, are within the scope of a nucleotide sequence corresponding to or having or as shown in a particular nucleotide sequence (i.e. the amino acid sequence encoded thereby remains the same). Such additions, deletions, and/or substitutions can be, for example, point mutations made according to methods known to those skilled in the art. It is also possible to substitute a nucleotide which alters the amino acid sequence encoded thereby, where the amino acid substituted is a conservative substitution or where amino acid homology is conserved. It is also possible to have minor nucleotide additions, deletions, and/or substitutions which do not alter the function of the resulting VSSC. Similarly, the term "corresponding to" or "having" or "as shown in" when used in conjunction with a SEQ ID NO for an amino acid sequence refers to an amino acid sequence which is substantially the same amino acid sequence or derivatives or equivalents thereof. Amino acid additions, deletions, and/or substitutions which do not negate the ability of the resulting protein to form a functional sodium channel are within the scope of an amino acid sequence corresponding to or having or as shown in a

particular amino acid sequence. Such additions, deletions, and/or substitutions can be, for example, the result of point mutations in the DNA encoding the amino acid sequence, such point mutations made according to methods known to those skilled in the art. Substitutions may be conservative substitutions of amino acids. As used herein, two amino acid residues are conservative substitutions of one another where the two residues are of the same type. In this regard, for purposes of the present invention, proline, alanine, glycine, serine, and threonine, all of which are neutral, weakly hydrophobic residues, are of the same type. Glutamine, glutamic acid, asparagine, and aspartic acid, all of which are acidic, hydrophilic residues, are of the same type. Another type of residue is the basic, hydrophilic amino acid residues, which include histidine, lysine, and arginine. Leucine, isoleucine, valine, and methionine all of which are hydrophobic, aliphatic amino acid residues, form yet another type of residue. Yet another type of residue consists of phenylalanine, tyrosine, and tryptophan, all of which are hydrophobic, aromatic residues. Further descriptions of the concept of conservative substitutions are given by French and Robson 1983, Taylor 1986, and Bordo and Argos 1991.

As further used herein, the term "corresponding to" or "having" or "as shown in" or "consisting of" when used in conjunction with a SEQ ID NO for a nucleotide or amino acid sequence is intended to cover linear or cyclic versions of the recited sequence (cyclic referring to entirely cyclic versions or versions in which only a portion of the molecule is cyclic, including, for example, a single amino acid cyclic upon itself), and is intended to cover derivative or modified nucleotides or amino acids within the recited sequence. For example, those skilled in the art will readily understand that an adenine

nucleotide could be replaced with a methyladenine, or a cytosine nucleotide could be replaced with a methylcytosine, if a methyl side chain is desirable. Nucleotide sequences having a given SEQ ID NO are intended to encompass nucleotide sequences containing these and like derivative or modified nucleotides, as well as cyclic variations. As a further example, those skilled in the art will readily understand that an asparagine residue could be replaced with an ethylasparagine if an ethyl side chain is desired, a lysine residue could be replaced with a hydroxylysine if an OH side chain is desired, or a valine residue could be replaced with a methylvaline if a methyl side chain is desired. Amino acid sequences having a given SEQ ID NO are intended to encompass amino acid sequences containing these and like derivative or modified amino acids, as well as cyclic variations. Cyclic, as used herein, also refers to cyclic versions of the derivative or modified nucleotides and amino acids.

The function of the encoded sodium channel can be assayed according to methods known in the art, such as by voltage clamp analysis of the channel following the functional expression of the channel in oocytes of the frog *Xenopus laevis* (see Taglialatela et al. 1992 and Stuhmer 1992 for a general discussion of the voltage clamp analysis of receptors and ion channels expressed in *Xenopus* oocytes). As used herein, "functional expression" refers to the synthesis and any necessary post-translational processing of a sodium channel molecule in a host cell so that the channel is inserted properly in the cell membrane and is capable of conducting sodium ions in response to an experimentally-imposed change in the cell membrane potential or upon exposure to appropriate pharmacological agents.

As further used herein, "sensitivity" and "resistance" refer to the relative responses of

genetically-defined insect populations to the paralytic or lethal actions of a test insecticide. For example, a dose of DDT [1,1-bis-(4-chlorophenyl)-2,2,2-trichloroethane] of approximately 0.02 μg per adult fly will kill approximately 50% of the treated individuals of a susceptible (Cooper-S) house fly strain, whereas doses of approximately 0.5 μg per adult fly are required to kill approximately 50% of the treated individuals of a resistant (538ge) house fly strain (Sawicki 1978). The absolute doses that define susceptibility and resistance vary with the insect species and genetically defined populations examined, the test insecticide employed, and the method of exposure. In general, an insect strain or population is considered "resistant" if it exhibits tolerance to a test insecticide (assessed as the dose required to poison 50% of a treated population or group) that is at least 10 times greater than the tolerance of an appropriate reference, or "susceptible" population. Test insecticides include not only DDT but also analogs of DDT (e.g., methoxychlor, perthane) and pyrethroid insecticides (e.g., deltamethrin, fenvalerate, resmethrin, permethrin).

As also used herein, insects include *Musca domestica* (the house fly), the fruit or vinegar fly (*Drosophila melanogaster*), and various other insect species of agricultural, medical or veterinary importance, such as *Heliothis virescens* (the tobacco budworm), *Leptinotarsa decemlineata* (the Colorado potato beetle), *Blattella germanica* (the German cockroach), and *Aedes aegypti* (the yellow fever mosquito).

The subject invention provides an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel (VSSC) of *Musca domestica*, wherein the VSSC is capable of conferring sensitivity or resistance to an insecticide in *Musca domestica*. The nucleic acid molecule can be deoxyribonucleic acid (DNA) or ribonucleic acid

(RNA, including messenger RNA or mRNA), genomic or recombinant, biologically isolated or synthetic.

The DNA molecule can be a cDNA molecule, which is a DNA copy of a messenger RNA (mRNA) encoding the VSSC.

In one embodiment, the VSSC confers insecticide susceptibility to *Musca domestica*. An example of such an insecticide susceptible VSSC is the channel encoded by the nucleotide sequence as shown in SEQ ID NO:1. SEQ ID NO:1 is the DNA sequence of one allele of the VSSC of *Musca domestica*. The amino acid sequence encoded by this allele is shown in SEQ ID NO:3.

In another embodiment, the VSSC confers insecticide resistance to *Musca domestica*. An example of such an insecticide resistant VSSC is the channel encoded by the nucleotide sequence as shown in SEQ ID NO:2. SEQ ID NO:2 is the DNA sequence of another allele of the VSSC of *Musca domestica* characteristic of the kdr insecticide resistant strain. The amino acid sequence encoded by this mutant allele is shown in SEQ ID NO:4.

The insecticide resistant allele preferably has the nucleotide sequence of a second nucleic acid molecule with one or more mutations therein, wherein the second nucleic acid molecule encodes an insecticide sensitive VSSC and wherein one or more mutations in the second nucleic acid molecule render the resulting VSSC resistant to an insecticide (hence the term "mutant" allele). In one embodiment, the mutant allele (having amino acid SEQ ID NO:4) has the amino acid sequence encoded by the susceptibility allele (amino acid SEQ ID NO:3) with amino acid differences as follows: a substitution of phenylalanine for leucine at amino acid residue 1014 of SEQ ID NO:3; a substitution of isoleucine for methionine at amino acid residue 1140 of SEQ ID NO:3; a substitution of aspartic acid for glycine at amino acid residue 2023 of SEQ ID NO:3; a deletion of amino acid residues 2031-2034

of SEQ ID NO:3 (glycine-alanine-threonine-alanine); a substitution of threonine for serine at amino acid residue 2042 of SEQ ID NO:3; a substitution of alanine for valine at amino acid residue 2054 of SEQ ID NO:3; and an insertion of three amino acid residues (asparagine-glycine-glycine) after amino acid residue 2055 of SEQ ID NO:3 (between amino acid residues 2055 and 2056 of SEQ ID NO:3). One or more of these amino acid differences can be included in an insecticide resistant VSSC. Other suitable sites for mutations can be identified by conventional, molecular genetic approaches, such as the identification of amino acid sequence substitutions/insertions/deletions in the VSSC sequences of other insecticide-resistant house fly strains.

The invention also provides an antisense nucleic acid molecule that is complementary to the mRNA encoding the VSSC, or a fragment thereof. Antisense nucleic acid molecules can be RNA or single-stranded DNA. Antisense molecules can be complementary to the entire DNA molecule encoding the VSSC, i.e. of the same nucleotide length as the entire molecule. It may be desirable, however, to work with a shorter molecule. In this instance, fragments of the entire antisense molecule can be used. Suitable fragments are capable of hybridizing to the mRNA encoding the entire molecule, and preferably consist of at least twenty nucleotides. These antisense molecules and fragments thereof can be used to reduce steady state levels of a VSSC gene product of *Musca domestica*, by introducing into cells an RNA or single-stranded DNA molecule that is complementary to the mRNA of the VSSC (i.e. by introducing an antisense molecule). The antisense molecule can base-pair with the mRNA of the VSSC, preventing translation of the mRNA into protein. Thus, an antisense molecule to the VSSC of *Musca domestica*

can prevent translation of mRNA encoding the VSSC into a functional sodium channel protein.

More particularly, an antisense molecule complementary to mRNA encoding a VSSC of *Musca domestica*, or a fragment thereof, can be used to decrease expression of a functional VSSC of *Musca domestica*. A cell with a first level of expression of a functional VSSC of *Musca domestica* is first selected, and then the antisense molecule (or fragment thereof) is introduced into the cell. The antisense molecule (or fragment thereof) blocks expression of functional VSSCs of *Musca domestica*, resulting in a second level of expression of a functional VSSC of *Musca domestica* in the cell. The second level is less than the initial first level.

Antisense molecules can be introduced into cells by any suitable means. Suitable cells include *Xenopus* oocytes which are useful host cells for studying the expression of the encoded sodium channel, and various insect cells, including but not limited to the insect cell lines *Drosophila Schneider* (Johansen et al. 1989), *Drosophila* K_c (Sang 1981), Sf9 (Smith et al. 1983), and High Five® (see U.S. Patent No. 5,300,435). In one embodiment, the antisense RNA molecule is injected directly into the cellular cytoplasm, where the RNA interferes with translation. A vector may also be used for introduction of the antisense molecule into a cell. Such vectors include various plasmid and viral vectors. For a general discussion of antisense molecules and their use, see Han et al. 1991 and Rossi 1995.

The invention further provides a special category of antisense RNA molecules, known as ribozymes, having recognition sequences complementary to specific regions of the mRNA encoding the VSSC of *Musca domestica*. Ribozymes not only complex with target sequences via complementary antisense sequences but also catalyze the

hydrolysis, or cleavage, of the template mRNA molecule. Examples, which are not intended to be limiting, of suitable regions of the mRNA template to be targeted by ribozymes are any of the regions encoding the 24 putative transmembrane domains of the VSSC of *Musca domestica*.

Expression of a ribozyme in a cell can inhibit gene expression (such as the expression of a VSSC of *Musca domestica*). More particularly, a ribozyme having a recognition sequence complementary to a region of a mRNA encoding a VSSC of *Musca domestica* can be used to decrease expression of a functional VSSC of *Musca domestica*. A cell with a first level of expression of a functional VSSC of *Musca domestica* is first selected, and then the ribozyme is introduced into the cell. The ribozyme in the cell decreases expression of a functional VSSC of *Musca domestica* in the cell, because mRNA encoding the VSSC is cleaved and cannot be translated.

Ribozymes can be introduced into cells by any suitable means. Suitable cells include *Xenopus* oocytes which are useful host cells for studying the expression of the encoded sodium channel, and various insect cells, including but not limited to the insect cell lines *Drosophila Schneider*, *Drosophila* K_c, Sf9, and High Five©. In one embodiment, the ribozyme is injected directly into the cellular cytoplasm, where the ribozyme cleaves the mRNA and thereby interferes with translation. A vector may be used for introduction of the ribozyme into a cell. Such vectors include various plasmid and viral vectors (note that the DNA encoding the ribozyme does not need to be "incorporated" into the genome of the host cell; it could be expressed in a host cell infected by a viral vector, with the vector expressing the ribozyme, for instance). For a general discussion of ribozymes and their use, see Sarver et al. 1990, Chrisey et al. 1991, Rossi et al. 1992, and Christoffersen et al. 1995.

The nucleic acid molecules of the subject invention can be expressed in suitable host cells using conventional techniques. Any suitable host and/or vector system can be used to express the VSSCs. These include, but are not limited to, eukaryotic hosts such as mammalian cells (i.e., Hela cells, Cv-1 cells, COS cells), *Xenopus* oocytes, and insect cells (i.e. insect cell lines such as *Drosophila Schneider, Drosophila* K_c, Sf9, and High Five®).

Techniques for introducing the nucleic acid molecules into the host cells may involve the use of expression vectors which comprise the nucleic acid molecules. These expression vectors (such as plasmids and viruses; viruses including bacteriophage) can then be used to introduce the nucleic acid molecules into suitable host cells. For example, sodium channel expression is often studied in *Xenopus* oocytes. DNA encoding the VSSC can be injected into the oocyte nucleus or transformed into the oocyte using a suitable vector, or mRNA encoding the VSSC can be injected directly into the oocyte, in order to obtain expression of a functional VSSC in the oocyte. It may be beneficial when expressing the sodium channels of the subject invention in *Xenopus* oocytes to coexpress a nucleic acid molecule encoding a tipE protein (Feng et al. 1995). Tip E has been found to be necessary to obtain expression of some sodium channels in *Xenopus* oocytes (Feng et al. 1995).

Various methods are known in the art for introducing nucleic acid molecules into host cells. One method is microinjection, in which DNA is injected directly into the nucleus of cells through fine glass needles (or RNA is injected directly into the cytoplasm of cells). Alternatively, DNA can be incubated with an inert carbohydrate polymer (dextran) to which a positively charged chemical group (DEAE, for diethylaminoethyl) has been coupled. The DNA sticks to the DEAE-dextran via its

negatively charged phosphate groups. These large DNA-containing particles stick in turn to the surfaces of cells, which are thought to take them in by a process known as endocytosis. Some of the DNA evades destruction in the cytoplasm of the cell and escapes to the nucleus, where it can be transcribed into RNA like any other gene in the cell. In another method, cells efficiently take in DNA in the form of a precipitate with calcium phosphate. In electroporation, cells are placed in a solution containing DNA and subjected to a brief electrical pulse that causes holes to open transiently in their membranes. DNA enters through the holes directly into the cytoplasm, bypassing the endocytotic vesicles through which they pass in the DEAE-dextran and calcium phosphate procedures (passage through these vesicles may sometimes destroy or damage DNA). DNA can also be incorporated into artificial lipid vesicles, liposomes, which fuse with the cell membrane, delivering their contents directly into the cytoplasm. In an even more direct approach, used primarily with plant cells and tissues, DNA is absorbed to the surface of tungsten microprojectiles and fired into cells with a device resembling a shotgun.

Several of these methods, microinjection, electroporation, and liposome fusion, have been adapted to introduce proteins into cells. For review, see Mannino and Gould-Fogerite 1988, Shigekawa and Dower 1988, Capecchi 1980, and Klein et al. 1987.

Further methods for introducing nucleic acid molecules into cells involve the use of viral vectors. Since viral growth depends on the ability to get the viral genome into cells, viruses have devised clever and efficient methods for doing it. One such virus widely used for protein production is an insect virus, baculovirus. Baculovirus attracted the attention of researchers because during infection, it produces one of

its structural proteins (the coat protein) to spectacular levels. If a foreign gene were to be substituted for this viral gene, it too ought to be produced at high level. Baculovirus, like vaccinia, is very large, and therefore foreign genes must be placed in the viral genome by recombination. To express a foreign gene in baculovirus, the gene of interest is cloned in place of the viral coat protein gene in a plasmid carrying a small portion of the viral genome. The recombinant plasmid is cotransfected into insect cells with wild-type baculovirus DNA. At a low frequency, the plasmid and viral DNAs recombine through homologous sequences, resulting in the insertion of the foreign gene into the viral genome. Virus plaques develop, and the plaques containing recombinant virus look different because they lack the coat protein. The plaques with recombinant virus are picked and expanded. This virus stock is then used to infect a fresh culture of insect cells, resulting in high expression of the foreign protein. For a review of baculovirus vectors, see Miller (1989). Various viral vectors have also been used to transform mammalian cells, such as bacteriophage, vaccinia virus, adenovirus, and retrovirus.

As indicated, some of these methods of transforming a cell require the use of an intermediate plasmid vector. U.S. Patent No. 4,237,224 to Cohen and Boyer describes the production of expression systems in the form of recombinant plasmids using restriction enzyme cleavage and ligation with DNA ligase. These recombinant plasmids are then introduced by means of transformation and replicated in unicellular cultures including procaryotic organisms and eucaryotic cells grown in tissue culture. The DNA sequences are cloned into the plasmid vector using standard cloning procedures known in the art, as described by Sambrook et al. (1989).

Host cells into which the nucleic acid encoding the VSSC has been introduced can be used to produce (i.e. to functionally express) the voltage-sensitive sodium channel.

Having identified the nucleic acid molecules encoding VSSCs and methods for expressing functional channels encoded thereby, the invention further provides a method of screening a chemical agent for the ability of the chemical agent to modify sodium channel function. The method comprises introducing a nucleic acid molecule encoding the VSSC into a host cell, and expressing the VSSC encoded by the molecule in the host cell. The expression results in the functional expression of a VSSC in the membrane of the host cell. The cell is then exposed to a chemical agent and evaluated to determine if the chemical agent modifies the function of the VSSC. From this evaluation, chemical agents effective in altering the function of the sodium channel can be found. Such agents may be, for example, tetrodotoxin, veratridine, and scorpion venom toxins. Additional agents can be found in Soderlund and Knipple 1994.

Cells transformed to include the VSSC according to the subject invention can be exposed to various potential insecticides and pesticides and evaluated for their susceptibility to the agents to develop and identify insect control agents that will not cause adverse effects to vertebrate species. Exemplary methods of screening are described in Eldefrawi et al. 1987 and Rauh et al. 1990. The evaluation of the function of the sodium channel can be by any means known in the art. In one embodiment, the evaluation comprises monitoring sodium transport through the VSSC. Sodium transport can be monitored by pre-incubating cells in a medium containing one or more chemical agents, adding a medium containing radiosodium ($^{22}Na^+$), incubating the cells further in this medium, and

isolating cells by filtration. Sodium transport is detected by the measurement of $^{22}Na^{+}$ within the cells by liquid scintillation counting or other radiometric techniques (Bloomquist and Soderlund 1988). Alternatively, [^{14}C]guanidinium ion can be employed as the radiotracer in the place of sodium using the same procedure (Jacques et al. 1978). In another embodiment, the function of the VSSC can be evaluated by pre-incubating cells to equilibrium with a sodium-selective fluorescent chelating agent (e.g., SBFI [sodium-binding benzofuran isophthalate]), washing the cells, exposing the cells to a test agent, and monitoring the increase in intracellular sodium by measuring the fluorescence of the SBFI-sodium complex (Deri and Adam-Vizi 1993).

The nucleic acid molecules of the subject invention can be used either as probes or for the design of primers to obtain DNA encoding other VSSCs by either cloning and colony/plaque hybridization or amplification using the polymerase chain reaction (PCR).

Specific probes derived from SEQ ID NOs 1 or 2 can be employed to identify colonies or plaques containing cloned DNA encoding a member of the VSSC family using known methods (see Sambrook et al. 1989). One skilled in the art will recognize that by employing such probes under high stringency conditions (for example, hybridization at 42°C with 5X SSPC and 50% formamide, washing at 50-65°C with 0.5X SSPC), sequences having regions which are greater than 90% identical to the probe can be obtained. Sequences with lower percent identity to the probe, which also encode VSSCs, can be obtained by lowering the stringency of hybridization and washing (for example, by reducing the hybridization and wash temperatures or reducing the amount of formamide employed).

More particularly, in one embodiment, the method comprises selection of a DNA molecule encoding a

VSSC of an insect, or a fragment thereof, the DNA molecule having a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, and designing an oligonucleotide probe for a VSSC based on SEQ ID NO:1 or SEQ ID NO:2. A genomic or cDNA library of an insect is then probed with the oligonucleotide probe, and clones are obtained from the library that are recognized by the oligonucleotide probe so as to obtain DNA encoding another VSSC.

Specific primers derived from SEQ ID NOs 1 or 2 can be used in PCR to amplify a DNA sequence encoding a member of the VSSC family using known methods (see Innis et al. 1990). One skilled in the art will recognize that by employing such primers under high stringency conditions (for example, annealing at 50-60°C, depending on the length and specific nucleotide content of the primers employed), sequences having regions greater than 75% identical to the primers will be amplified.

More particularly, in a further embodiment the method comprises selection of a DNA molecule encoding a VSSC of an insect, or a fragment thereof, the DNA molecule having a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, designing degenerate oligonucleotide primers based on regions of SEQ ID NO:1 or SEQ ID NO:2, and employing such primers in the polymerase chain reaction using as a template a DNA sample to be screened for the presence of VSSC-encoding sequences. The resulting PCR products can be isolated and sequenced to identify DNA fragments that encode polypeptide sequences corresponding to the targeted region of a VSSC.

Various modifications of the nucleic acid and amino acid sequences disclosed herein are covered by the subject invention. These varied sequences still encode a functional VSSC. The invention thus further provides an

isolated nucleic acid molecule encoding a VSSC of an insect, the nucleic acid molecule encoding a first amino acid sequence having at least 95% amino acid identity to a second amino acid sequence, the second amino acid sequence being as shown in SEQ ID NO:3. The resulting encoded VSSC is susceptible to an insecticide. The invention also provides an isolated nucleic acid molecule encoding a VSSC of an insect, the nucleic acid molecule encoding a first amino acid sequence having at least 95% amino acid identity to a second amino acid sequence, the second amino acid sequence being as shown in SEQ ID NO:4. The resulting VSSC is resistant to an insecticide.

The invention further provides isolated voltage-sensitive sodium channels of *Musca domestica*, wherein the VSSC is capable of conferring sensitivity or resistance to an insecticide in *Musca domestica*. In one embodiment, the VSSC confers susceptibility to an insecticide in *Musca domestica*, such as the VSSC encoded by the nucleotide sequence as shown in SEQ ID NO:1 (which encodes an amino acid sequence as shown in SEQ ID NO:3). In a further embodiment, the VSSC confers resistance to an insecticide in *Musca domestica*, such as the VSSC encoded by the nucleotide sequence as shown in SEQ ID NO:3 (which encodes an amino acid sequence as shown in SEQ ID NO:4). Preferably, the insecticide resistant VSSC is encoded by a nucleic acid molecule having the nucleotide sequence of a second nucleic acid molecule with one or more mutations therein, wherein the second nucleic acid molecule encodes an insecticide sensitive VSSC, and wherein the one or more mutations in the second nucleic acid molecule render the resulting voltage-sensitive sodium channel resistant to an insecticide. For example, the nucleotide sequence of the second nucleic acid molecule may encode amino acid SEQ ID NO:3, and the insecticide resistant VSSC may have that amino acid sequence with one or more differences therein

as follows: a substitution of phenylalanine for leucine at amino acid residue 1014 of SEQ ID NO:3; a substitution of isoleucine for methionine at amino acid residue 1140 of SEQ ID NO:3; a substitution of aspartic acid for glycine at amino acid residue 2023 of SEQ ID NO:3; a deletion of amino acid residues 2031-2034 of SEQ ID NO:3 (glycine-alanine-threonine-alanine); a substitution of threonine for serine at amino acid residue 2042 of SEQ ID NO:3; a substitution of alanine for valine at amino acid residue 2054 of SEQ ID NO:3; and an insertion of three amino acid residues (asparagine-glycine-glycine) after amino acid residue 2055 of SEQ ID NO:3 (between amino acid residues 2055 and 2056 of SEQ ID NO:3).

A variety of methodologies known in the art can be utilized to obtain an isolated VSSC according to the subject invention. In one method, the channel protein is purified from tissues or cells which naturally produce the channel protein. One skilled in the art can readily follow known methods for isolating proteins in order to obtain a member of the VSSC protein family, free of natural contaminants. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immunoaffinity chromatography. In another embodiment, a member of the VSSC family can be purified from cells which have been altered to express the channel protein. As used herein, a cell is said to be "altered to express the channel protein" when the cell, through genetic manipulation, is made to produce the channel protein which it normally does not produce or which the cell normally produces at low levels. One skilled in the art can readily adapt procedures for introducing and expressing either genomic, cDNA or synthetic sequences into either eukaryotic or prokaryotic cells in order to generate a

cell which produces a member of the VSSC family utilizing the sequences disclosed herein.

A VSSC as defined herein includes molecules encoding VSSCs encoded by an amino acid sequence having at least 95% amino acid identity to SEQ ID NO:3 or to SEQ ID NO:4.

Antibodies can be raised to the voltage-sensitive sodium channel. Antibodies of the subject invention include polyclonal antibodies and monoclonal antibodies capable of binding to the channel protein, as well as fragments of these antibodies, and humanized forms. Humanized forms of the antibodies of the subject invention may be generated using one of the procedures known in the art such as chimerization. Fragments of the antibodies of the present invention include, but are not limited to, the Fab, the Fab2, and the Fd fragments.

The invention also provides hybridomas which are capable of producing the above-described antibodies. A hybridoma is an immortalized cell line which is capable of secreting a specific monoclonal antibody.

In general, techniques for preparing polyclonal and monoclonal antibodies as well as hybridomas capable of producing the desired antibody are well known in the art (see Campbell 1984 and St. Groth et al. 1980). Any animal (mouse, rabbit, etc.) which is known to produce antibodies can be immunized with the antigenic channel protein (or an antigenic fragment thereof). Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the protein. One skilled in the art will recognize that the amount of the channel protein used for immunization will vary based on the animal which is immunized, the antigenicity of the protein, and the site of injection.

The protein which is used as an immunogen may be modified or administered in an adjuvant in order to

increase the protein's antigenicity. Methods of increasing the antigenicity of a protein are well known in the art and include, but are not limited to, coupling the antigen with a heterologous protein (such as a globulin or beta-galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/O-Ag 15 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells.

Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, western blot analysis, or radioimmunoassay (Lutz et al. 1988).

Hybridomas secreting the desired antibodies are cloned and the class and subclass are determined using procedures known in the art (Campbell 1984).

For polyclonal antibodies, antibody containing antisera is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures.

The present invention further provides the above-described antibodies in detectably labeled form. Antibodies can be detectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, etc.), enzymatic labels (such as horseradish peroxidase, alkaline phosphatase, etc.), fluorescent labels (such as FITC or rhodamine, etc.), paramagnetic atoms, etc. Procedures for accomplishing such labeling are well known in the art, for example see Sternberger et al. 1970, Bayer et al. 1979, Engval et al. 1972, and Goding 1976.

The labeled antibodies or fragments thereof of the present invention can be used for in vitro, in vivo,

and in situ assays to identify cells or tissues which express a VSSC, to identify samples containing the VSSC proteins, or to detect the presence of a VSSC in a sample. More particularly, the antibodies or fragments thereof can thus be used to detect the presence of a VSSC in a sample, by contacting the sample with the antibody or fragment thereof. The antibody or fragment thereof binds to any VSSC present in the sample, forming a complex therewith. The complex can then be detected, thereby detecting the presence of the VSSC in the sample.

Fragments of the nucleic acid molecules encoding a VSSC are also provided, and are best defined in the context of amino acid sequence relationships among members of the VSSC sequence family and information on the function of specific VSSC domains. For example the amino acid sequence encoded by nucleotides 4648-4803 of SEQ ID NOs 1 or 2 encodes an amino acid sequence that is highly conserved among VSSC family members and is identified as the structural component forming the "inactivation gate" of sodium channels. Antibodies prepared to the polypeptide encoded by this fragment would therefore be expected to be of use as reagents capable of detecting many members of the VSSC family. Such antibodies, if introduced into cells that express VSSCs, would also be expected to modify the normal function of the VSSCs expressed in those cells. In contrast, the amino acid sequence encoded by nucleotides 3079-3852 of SEQ ID NOs 1 or 2 encodes an amino acid sequence that is less well conserved between the VSSCs of the insects *Musca domestica* and *Drosophila melanogaster*. Antibodies prepared to the polypeptide encoded by this fragment would therefore be expected to recognize selectively the VSSC from which the fragment was derived.

Also provided by the subject invention is a plasmid designated pPJI1 and deposited with the ATCC under

Accession No.______, as well as a KpnI/AatII restriction fragment of about 3620 bp of the plasmid designated pPJI1. Further provided is a plasmid designated pPJI2 and deposited with the ATCC under Accession No. _____, as well as an AatII/SphII restriction fragment of about 2700 bp of the plasmid designated pPJI2. When the above two restriction fragments are ligated together at their AatII sites, the resulting nucleic acid molecule encodes a voltage-sensitive sodium channel which confers susceptibility to an insecticide in *Musca domestica*. This resulting nucleic acid molecule is also provided by the subject invention.

MATERIALS AND METHODS

Heads of newly-emerged adult house flies (NAIDM or 538ge strain) (Knipple et al. 1994) were ground to a fine powder under liquid N_2 and extracted with acid guanidinium isothiocyanate/phenol/chloroform to obtain total RNA (Chomczynski and Sacchi 1987), which was fractionated on oligo(dT)-paramagnetic beads (PolyATtract mRNA isolation system; Promega, Madison, WI) to obtain poly(A^+) RNA. Pools of first strand cDNA were synthesized using either random hexamers (Harvey and Darlison 1991) or oligo(dT) adapted for the 3'-RACE procedure (Frohman and Martin 1989). These cDNA pools were employed as templates in the polymerase chain reaction (PCR) (Saiki et al. 1988) to amplify overlapping cDNA segments spanning the entire *Vssc1* coding sequence. Mixed-sequence oligonucleotide primers employed for these amplifications comprised all possible sequence combinations encoding short (i.e., 6-8 residues) regions of amino acid conservation between the *para* gene of D. *melanogaster* and rat brain sodium channel I (Loughney et al. 1989; Knipple et al. 1991). In a few cases, mixed-sequence primers were based solely on the *D. melanogaster* sequence. Defined-sequence primers were

derived either from the previously described 309-nucleotide exon of the house fly *Vssc1* gene (Knipple et al. 1994) or from internal sequences of house fly cDNA fragments obtained by amplification with mixed-sequence primers. All primers were synthesized using an Applied Biosystems 392 instrument, deprotected using procedures provided by Applied Biosystems, desalted, and used without further purification. The sequences and designations of these primers are given in Table I. The methods and reagents employed in PCR amplifications are described elsewhere (Knipple et al. 1991; Henderson et al. 1994; Knipple et al. 1994); specific amplification conditions for each cDNA fragment were optimized by varying the annealing temperatures and extension times of the reaction. Following amplification, PCR products were separated from excess primers either by filtration of the reaction mixture through a Centricon-100 concentrator (Amicon, Beverly, MA) or by preparative electrophoresis on agarose gels, excision of the desired product, and extraction from the gel matrix (QIAquick spin column; Qiagen, Chatsworth, CA) prior to use as templates for DNA sequencing.

The DNA sequences of amplified cDNA fragments were determined by automated sequencing with an Applied Biosystems 373 instrument using fluorescently-labeled dideoxynucleotides and *Taq* DNA polymerase (PCR/Sequencing Kit; Applied Biosystems, Foster City, CA) in a modification of the dideoxynucleotide chain-termination method (Sanger et al. 1977). Sequencing of each amplification product was initiated by using the amplification primers to sequence inward from the termini, and additional primers were synthesized as needed to obtain the complete sequence of each strand. Mixed-sequence amplification primers were employed for sequencing at concentrations 10-fold higher than that used

for defined-sequence primers. All sequence ambiguities and apparent polymorphisms were resolved by performing additional multiple sequencing reactions. The full-length *Vssc1* coding sequences from the NAIDM and 538ge strains were compiled from 239 and 209 individual sequencing reactions, respectively, and were edited using the SeqEd software program (Applied Biosystems). Complete house fly *Vssc1* sequences were analyzed and compared with published sodium channel sequences using the DNASTAR software package (DNASTAR, Madison, WI).

EXAMPLE I

SEQUENCING OF THE INSECTICIDE SENSITIVE VSSC OF HOUSE FLY

As an expedient alternative to conventional iterative screenings of cDNA libraries, a sequencing strategy for the house fly *Vssc1* gene was based on the PCR amplification and direct automated sequencing of overlapping cDNA fragments (Fig. 2). The point of entry for this strategy was the 309-nucleotide exon of the house fly *Vssc1* gene identified previously from sequencing of cloned genomic DNA (Knipple et al. 1994). The use of defined-sequence primers from this region (Table I, A1 or B2) in combination with mixed-sequence primers encoding conserved amino acid sequences in either region IIS3 (A2) or the extracellular *N*-terminal domain (B1) gave cDNA fragments **A** and **B**. A second point of entry was established in homology domain IV using a pair of mixed-sequence primers (C1 and C2) to obtain fragment **C**. A primer (D2) designed from the internal sequence of fragment **C**, together with a mixed-sequence primer (D1) encoding a conserved amino acid motif in the short linker between homology domains III and IV, gave fragment **D**. A pair of

defined-sequence primers (E1, E2) based on internal sequences of fragments **A** and **D** gave the large fragment **E**, which spanned most of homology domain II and all of homology domain III. Fragment **F**, corresponding to the 5′ end of the coding sequence, was obtained using a defined-sequence primer (F2) derived from the internal sequence of fragment **B** and a mixed-sequence primer (F1) derived from a segment of the *D. melanogaster* sequence upstream from the translation start site (Loughney et al. 1989). Similarly, fragment **G**, containing the 3′ end of the coding sequence, was obtained using a defined-sequence primer (G1) derived from the internal sequence of fragment **C** and a mixed-sequence primer (G2) derived from a segment of the *D. melanogaster* sequence downstream from the stop codon (Thackeray and Ganetzky 1994).

The complete coding sequence of the *Vssc1*^{NAIDM} allele of the house fly, comprising a single open reading frame of 6318 nucleotides (SEQ ID NO:1), was determined by automated DNA sequencing using cDNA fragments **A** - **G** as templates (Fig. 2). This cDNA coded for a 2105-amino acid polypeptide (SEQ ID NO:3) with a predicted molecular weight of 236,671 Daltons that exhibited all of the common structural landmarks found in sodium channel α subunit genes (Catterall 1992; Kallen et al. 1993) (see Fig. 3), including four large internally homologous subdomains (I-IV), each containing six hydrophobic putative transmembrane helices (S1-S6) and a conserved sequence element between domains S5 and S6 identified as an ion pore-forming domain. The deduced *Vssc1*^{NAIDM} amino acid sequence also contained a conserved element in the S4 region of each homology domain, characterized by a repeated motif of positively-charged amino acids that are thought to form the voltage-sensing element of the channel, and a short segment of conserved sequence between homology domains III and IV that has been identified as

the channel inactivation gate (see Fig. 3). The deduced *Vssc1*^{NAIDM} protein contained 10 potential sites for *N*-linked glycosylation (Kornfeld and Kornfeld 1985), 6 of which occur in putative extracellular regions. These regions of other sodium channel α subunit sequences are also known to contain potential glycosylation sites (Catterall 1992; Kallen et al. 1993).

Vertebrate sodium channels are known to undergo functional regulation as the result of phosphorylation by cAMP-dependent protein kinases at sites in the intracellular linker between homology domains I and II and by protein kinase C at a site in the intracellular linker between homology domains III and IV (Catterall 1992; Kallen et al. 1993). The deduced *Vssc1*^{NAIDM} protein contained three potential cAMP-dependent protein kinase phosphorylation sites (Kemp and Pearson 1990) (Ser540, Ser557, and Ser628) in the cytoplasmic linker between homology domains I and II. The location of two of these (Ser540 and Ser557 of SEQ ID NO:3) corresponded to the cluster of four sites found in this region of vertebrate brain sodium channels that are implicated in sodium channel regulation (Catterall 1992). The deduced *Vssc1*^{NAIDM} protein also contained three additional potential phosphorylation sites (Ser1167, Ser1207, and Ser2097 of SEQ ID NO:3) in other putative intracellular domains. The role of these phosphorylation sites in the regulation of insect sodium channels by cAMP-dependent protein kinase is not known. The deduced house fly voltage-sensitive sodium channel protein also contained two potential sites for protein kinase C phosphorylation (Ser1191 and Ser1582 of SEQ ID NO:3) (Kemp and Pearson 1990), the latter of which is the conserved site located within the inactivation gate sequence of the cytoplasmic linker between domains III and IV. Although the conservation of this site implicates a role for protein kinase C in the regulation of insect

sodium channels, such an effect has not been demonstrated experimentally.

The deduced *Vssc1*^{NAIDM} protein was 90.0% identical to the most similar variant of the *para* gene product of *D. melanogaster* (SEQ ID NO:19) (Loughney et al. 1989; Thackeray and Ganetzky 1994) (Fig. 3). The level of sequence identity was highest (≥95%) in the *N*-terminal intracellular domain, the linker between homology domains III and IV, and homology domain IV. The level of sequence identity was lowest (73%) in the intracellular *C*-terminal domain. Alignment of the *Vssc1* sequence with 12 other sodium channel α subunit sequences found in the GenBank database showed that the *Vssc1* and *para* gene products exhibited approximately the same degree of sequence similarity as homologous sodium channel α subunit isoforms from different vertebrate species. These findings confirm and extend previous observations (Williamson et al. 1993; Knipple et al. 1994), based on fragmentary genomic DNA and cDNA sequences, of the high degree of sequence similarity between this house fly gene and the *para* gene of *D. melanogaster* and reinforce the conclusion that *Vssc1* is the homolog of *para* in the house fly.

In *D. melanogaster* (Thackeray and Ganetzky 1994; O'Dowd et al. 1995) and *Drosophila virilis* (Thackeray and Ganetzky 1995), multiple sodium channel α subunit variants, each under specific developmental regulation, are generated from the *para* gene by the alternative usage of 8 exons (designated *a-f, h,* and *i*) located in homology domain II and portions of the cytoplasmic linker regions on either side of this domain. Given the heterogeneity of sodium channel-encoding sequences found in these Dipteran species, it was surprising to detect only a single sequence variant among the pool of amplified house fly head cDNA fragments. The *Vssc1*^{NAIDM} sequence contained segments identical to exon *a*

and homologous (21 identical amino acids out of 24) to exon *i* of *D. melanogaster*. Recent studies suggest that both of these exons are required for the expression of high sodium current densities in embryonic *D. melanogaster* neurons (O'Dowd *et al.* 1995). In the region encoded by either exon *c* or exon *d*, the house fly sequence differs from both *D. melanogaster* sequences but is slightly more similar to exon *d* (50 identical amino acids out of 55) than to exon *c* (49 identical amino acids out of 55). The house fly sequence lacked segments homologous to *D. melanogaster* exons *b*, *e*, and *f* but contained a segment identical to exon *h*, which is a variable element found in some *D. virilis* sequences but not detected in *D. melanogaster*. The house fly $\mathit{Vssc1}^{\mathrm{NAIDM}}$ sequence described is thus characterized as structurally homologous to the $a^{+}b^{-}c^{-}d^{+}e^{-}f^{-}h^{+}i^{+}$ splice variant of *D. melanogaster* and *D. virilis*. The identification of this molecular form as the predominant sodium channel sequence variant in house fly heads was unexpected because it has not been detected among the arrays of splice variants detected in whole embryos or whole adults of either *D. melanogaster* or *D. virilis*.

EXAMPLE II

SEQUENCING OF THE INSECTICIDE RESISTANT VSSC OF HOUSE FLY

The PCR amplification/ sequencing strategy summarized in Fig. 2 was also employed to determine the sequence of *Vssc1* cDNAs from heads of the 538ge house fly strain that carries the *kdr* trait. The nucleotide sequence of the VSSC of the 538ge house fly is shown in SEQ ID NO:2, and the amino acid sequence is shown in SEQ ID NO:4. The amino acid sequence of 2104 residues (SEQ ID

NO:4) encoded by the *Vssc1*^{538ge} cDNA contained 12 amino acid differences compared to that of the *Vssc1*^{NAIDM} sequence (SEQ ID NO:3) as follows: a substitution of phenylalanine for leucine at amino acid residue 1014 of SEQ ID NO:3; a substitution of isoleucine for methionine at amino acid residue 1140 of SEQ ID NO:3; a substitution of aspartic acid for glycine at amino acid residue 2023 of SEQ ID NO:3; a deletion of amino acid residues 2031-2034 of SEQ ID NO:3 (glycine-alanine-threonine-alanine); a substitution of threonine for serine at amino acid residue 2042 of SEQ ID NO:3; a substitution of alanine for valine at amino acid residue 2054 of SEQ ID NO:3; and an insertion of three amino acid residues (asparagine-glycine-glycine) after amino acid residue 2055 of SEQ ID NO:3 (between amino acid residues 2055 and 2056 of SEQ ID NO:3). A comparison of the *Vssc1*^{538ge} (SEQ ID NO:4) and *Vssc1*^{NAIDM} (SEQ ID NO:3) amino acid sequences to the *para* sequence of the Canton-S strain of *D. melanogaster* (SEQ ID NO:19) is shown in Fig. 3. The locations and amino acid sequence context of the differences are shown in Fig. 4. In Fig. 4, S refers to the NAIDM amino acid sequence (SEQ ID NO:3), and R refers to the kdr sequence (SEQ ID NO:4). Dashes indicate that the Kdr sequence has the identical residue at that position as does the NAIDM sequence. The difference labeled 1 shows amino acids 1009-1019 of SEQ ID NO:3, with the amino acid substitution at residue 1014 shown. The difference labeled 2 shows amino acids 1135-1145 of SEQ ID NO:3, with the amino acid substitution at residue 1140 shown. The difference labeled 3 shows amino acids 2018-2028 of SEQ ID NO:3, with the amino acid substitution at residue 2023 shown. The difference labeled 4 shows amino acids 2027-2038 of SEQ ID NO:3, with the deletion of residues 2031-2034 shown. The difference labeled 5 shows amino acids 2037-2047 of SEQ ID NO:3, with the amino acid substitution at residue 2042 shown. The

difference labeled 6 shows amino acids 2051-2059 of SEQ ID NO:3, with the amino acid substitution at residue 2054 shown and the insertion of three residues between 2055 and 2056 shown.

Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow.

Table 1. Names and sequences of oligonucleotide primers used in the PCR amplification of partial *Vssc1* cDNAs.

Name	Sequence	
A1	5'-CGGTTGGGCTTTCCTGTC-3'	SEQ ID NO:5
A2	5'-GGGAATTCRAADATRTTCCANCCYTC-3'	SEQ ID NO:6
B1	5'-CCCGARGAYATHGAYCYNTAYTA-3'	SEQ ID NO:7
B2	5'-CGTATCGCCTCCTCCTCG-3'	SEQ ID NO:8
C1	5'-GGGTCTAGATHTTYGCNATHTTYGGNATG'3'	SEQ ID NO:9
C2	5'-GGGGAATTCNGGRTCRAAYTGYTGCCA-3'	SEQ ID NO:10
D1	5'-GGGTCTAGARGANCARAARAARTAYTA-3'	SEQ ID NO:11
D2	5'-TCATACTTTGGCCCAATGTC-3'	SEQ ID NO:12
E1	5'-CCCGAATTAGAGAAGGTGCTG-3'	SEQ ID NO:13
E2	5'-ACTATTGCTTGTGGTCGCCAC-3'	SEQ ID NO:14
F1	5'-CATCNTTRGCNGCNTAGACNATGAC-3'	SEQ ID NO:15
F2	5'-GATTGAATGGATCGAGCAGCC-3'	SEQ ID NO:16
G1	5'-CGTTTCTCCTTTCATATCTAG-3'	SEQ ID NO:17
G2	5'-GGAGBGGBGGNCKBGGNCKNGCTCA-3'	SEQ ID NO:18

Designation of oligonucleotide mixtures: B=G+T+C; D=G+A+T; H=A+T+C; K=G+T; N=A+C+G+T; R=A+G; Y=C+T.

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6318 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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GGTCCACAGC CGGATCCCAC ACTTGAACAG GGTGTGCCTA TACCTGTTCG AATGCAGGGC 240

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GGCGACATGA TGTACTGTGT GGATATATTG GATGCCCTGA CCAAGGACTT CTTTGCGCGC 5820

AAGGGTAATC CGATCGAGGA GACGGGTGAA ATTGGTGAGA TAGCGGCGCG ACCGGACACC 5880

GAGGGCTATG ATCCGGTGTC GTCAACACTG TGGCGCCAGC GTGAGGAGTA CTGCGCCAAG 5940

CTGATACAGA ATGCGTGGCG GCGTTACAAG AATGGCCCAC CCCAGGAGGG TGATGAGGGC 6000

GAGGCGGCTG GTGGCGAAGA TGGTGCTGAA GGCGGTGAGG GTGAAGGAGG CAGCGGCGGC 6060

GGCGGCGGTG ATGATGGTGG CTCAGCGACA GGAGCAACGG CGGCGGCGGG AGCCACATCA 6120

CCCTCAGATC CAGATGCCGG CGAAGCAGAT GGTGCCAGCG TCGGCGGCCC CCTTAGTCCG 6180

GGCTGTGTTA GTGGCGGCAG TAATGGCCGC CAAACGGCCG TACTGGTCGA AAGCGATGGT 6240

TTTGTTACAA AAAACGGTCA TAAGGTTGTA ATACACTCGA GATCGCCGAG CATAACATCC 6300

AGGACGGCAG ATGTCTGA 6318

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6315 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGACAGAAG ATTCCGACTC GATATCTGAG GAAGAACGCA GTTTGTTCCG TCCCTTCACC 60

CGCGAATCAT TGTTACAAAT CGAACAACGT ATCGCTGAAC ATGAAAAACA AAAGGAGCTG 120

GAAAGAAAGA GAGCCGCCGA AGGAGAGCAG ATACGATATG ATGACGAGGA CGAAGATGAA 180
GGTCCACAGC CGGATCCCAC ACTTGAACAG GGTGTGCCTA TACCTGTTCG AATGCAGGGC 240
AGCTTCCCGC CGGAATTGGC CTCCACTCCT CTCGAGGATA TCGATCCCTT CTACAGTAAT 300
GTACTGACAT TTGTAGTAAT AAGTAAAGGA AAGGATATTT TTCGTTTTTC TGCCTCAAAA 360
GCAATGTGGC TGCTCGATCC ATTCAATCCG ATACGTCGTG TAGCCATTTA TATTTTAGTG 420
CATCCCTTGT TTTCGTTATT CATTATCACC ACTATTCTAA CTAATTGTAT TTTAATGATA 480
ATGCCGACAA CGCCCACGGT CGAATCCACA GAGGTGATAT TCACCGGAAT CTACACATTT 540
GAATCAGCTG TTAAAGTGAT GGCACGAGGT TTCATTTTAT GCCCGTTTAC GTATCTTAGA 600
GATGCATGGA ATTGGCTGGA CTTCGTAGTA ATAGCTTTAG CTTATGTGAC CATGGGCATA 660
GATTTAGGTA ATCTCGCAGC TTTGAGAACA TTTAGGGTAC TGCGAGCTCT GAAAACCGTA 720
GCCATTGTGC CAGGTCTAAA AACCATTGTC GGTGCTGTCA TTGAATCTGT AAAAAATCTA 780
CGCGATGTGA TAATTTTGAC AATGTTTTCC CTGTCGGTGT TCGCGCTGAT GGGCCTACAA 840
ATCTATATGG GTGTTCTAAC ACAAAAGTGC ATTAAACGAT TCCCCCTGGA CGGCAGTTGG 900
GGCAATCTGA CCGATGAAAA CTGGTTTCTA CACAATAGCA ACAGTTCCAA TTGGTTTACG 960
GAGAACGATG GCGAGTCATA TCCGGTGTGC GGGAATGTAT CCGGTGCGGG ACAATGCGGC 1020
GAAGATTACG TCTGCCTGCA GGGCTTCGGC CCCAATCCCA ACTACGACTA CACCAGTTTC 1080
GACTCATTCG GTTGGGCTTT CCTGTCGGCG TTTCGTCTCA TGACCCAAGA TTTCTGGGAG 1140
GATCTGTATC AGCACGTGCT GCAAGCAGCT GGACCCTGGC ACATGTTGTT CTTTATAGTC 1200
ATCATCTTCC TAGGTTCATT CTATCTTGTG AATTTGATTT TGGCCATTGT TGCCATGTCT 1260
TATGACGAAT TGCAAAAGAA GGCCGAAGAA GAAGAGGCTG CCGAGGAGGA GGCGATCCGA 1320
GAAGCTGAAG AAGCGGCAGC AGCCAAGGCG GCCAAACTGG AGGAGCGGGC CAATGTAGCA 1380
GCTCAAGCGG CTCAGGATGC AGCGGATGCC GCTGCGGCAG CTCTGCATCC CGAGATGGCA 1440
AAGAGTCCCA CGTACTCTTG CATTAGCTAT GAACTGTTTG TTGGCGGCGA GAAGGGCAAC 1500
GATGACAACA ACAAGGAGAA GATGTCGATA CGCAGCGTCG AAGTGGAATC GGAGTCGGTG 1560

AGCGTTATAC AAAGACAACC AGCACCTACC ACAGCACCCG CTACTAAAGT CCGTAAAGTT 1620

AGCACGACTT CCTTATCCTT ACCTGGTTCA CCATTTAACC TACGCCGGGG ATCACGTAGT 1680

TCACACAAGT ACACAATACG AAATGGGCGT GGACGTTTTG GTATACCAGG TAGCGATCGC 1740

AAGCCATTGG TACTGCAAAC ATATCAGGAT GCCCAGCAGC ATTTGCCCTA TGCCGATGAC 1800

TCGAATGCCG TAACACCAAT GTCCGAAGAG AATGGTGCCA TTATAGTACC AGCCTACTAT 1860

TGTAATTTAG GTTCTAGACA TTCTTCATAT ACCTCGCATC AATCAAGAAT CTCGTATACA 1920

TCACATGGTG ATTTATTGGG TGGCATGGCG GCCATGGGTG CCAGCACAAT GACCAAAGAG 1980

AGCAAATTGC GCAGTCGCAA CACACGCAAT CAATCAATCG GTGCTGCAAC CAATGGTGGC 2040

AGTAGTACGG CCGGTGGTGG CTATCCCGAT GCCAATCACA AGGAACAAAG GGATTATGAA 2100

ATGGGTCAGG ATTATACAGA CGAAGCTGGC AAAATAAAAC ACCACGACAA TCCTTTTATC 2160

GAGCCCGTCC AAACTCAAAC AGTGGTAGAC ATGAAAGATG TTATGGTCTT AAATGATATC 2220

ATTGAACAAG CCGCTGGTCG GCATAGTCGT GCTAGTGAAC GAGGTGAGGA CGATGACGAA 2280

GATGGTCCCA CATTCAAGGA CATCGCCCTC GAATATATCC TAAAAGGCAT CGAAATCTTT 2340

TGTGTATGGG ACTGTTGTTG GGTGTGGTTA AAATTTCAGG AATGGGTCTC CTTTATTGTG 2400

TTCGATCCAT TCGTGGAGCT CTTCATTACC CTGTGTATTG TGGTCAATAC AATGTTCATG 2460

GCCATGGATC ATCACGACAT GAATCCGGAA TTGGAGAAGG TGCTGAAAAG TGGTAACTAT 2520

TTCTTCACGG CCACTTTTGC AATTGAGGCC AGCATGAAAC TGATGGCCAT GAGCCCGAAG 2580

TACTACTTCC AGGAAGGCTG GAACATTTTC GATTTCATTA TTGTGGCCTT GTCTCTGCTG 2640

GAATTGGGCC TGGAGGGTGT CCAGGGCCTG TCGGTGTTGA GAAGTTTTCG TTTGCTTCGT 2700

GTATTCAAAT TGGCAAAATC ATGGCCCACA CTGAATTTAC TCATTTCGAT TATGGGCCGG 2760

ACAATGGGTG CATTGGGTAA TCTGACATTT GTACTTTGCA TTATCATCTT CATCTTTGCC 2820

GTGATGGGAA TGCAACTTTT CGGAAAGAAC TATATTGACC ACAAGGATCG CTTCAAGGAC 2880

CATGAATTAC CGCGCTGGAA TTTCACCGAC TTCATGCACA GCTTCATGAT TGTGTTCCGA 2940

GTGCTGTGCG GAGAGTGGAT CGAGTCCATG TGGGACTGCA TGTATGTGGG CGATGTCAGC 3000

TGTATACCCT TCTTCTTGGC CACGGTCGTG ATCGGCAATT TTGTGGTTCT TAATCTTTTC 3060

TTAGCTTTGC TTTTGTCCAA CTTCGGTTCA TCTAGTTTAT CAGCCCCGAC TGCCGACAAT 3120

GATACCAATA AAATAGCAGA GGCCTTCAAT CGTATTGCTC GTTTTAAGAA CTGGGTGAAA 3180

CGTAATATTG CCGATTGTTT TAAGTTAATT CGAAATAAAT TGACAAATCA AATAAGTGAC 3240

CAACCATCAG AACATGGCGA TAATGAACTG GAGTTGGGTC ATGACGAAAT CATGGGCGAT 3300

GGCTTGATCA AAAAGGGTAT GAAGGGCGAG ACCCAGCTGG AGGTGGCCAT TGGCGATGGC 3360

ATGGAGTTCA CGATACATGG CGATATGAAA AACAACAAGC CCAAGAAATC AAAATTCATA 3420

AACAACACAA CGATGATTGG AAACTCAATA AACCACCAAG ACAATAGACT GGAACATGAG 3480

CTAAACCATA GAGGTTTGTC CATACAGGAC GATGACACTG CCAGCATTAA CTCATATGGT 3540

AGCCATAAGA ATCGACCATT CAAGGACGAG AGCCACAAGG GCAGCGCCGA GACCATCGAG 3600

GGCGAGGAGA AACGCGACGT CAGCAAAGAG GACCTCGGCC TCGACGAGGA ACTGGACGAG 3660

GAGGCCGAGG GCGATGAGGG CCAGCTGGAT GGTGACATCA TCATTCATGC CCAAAACGAC 3720

GACGAGATAA TCGACGACTA TCCGGCCGAC TGTTTCCCCG ACTCGTACTA CAAGAAGTTT 3780

CCGATCTTGG CCGGCGACGA GGACTCGCCG TTCTGGCAAG GATGGGGCAA TTTACGACTG 3840

AAAACTTTTC AATTAATTGA AAATAAATAT TTTGAAACCG CAGTTATCAC TATGATTTTA 3900

ATGAGTAGCT TAGCTTTGGC CTTAGAAGAT GTTCATTTAC CCGATCGACC TGTCATGCAG 3960

GATATACTGT ACTACATGGA CAGGATATTT ACGGTGATAT TCTTTTTGGA GATGTTGATC 4020

AAATGGTTGG CCCTGGGCTT TAAGGTCTAC TTCACCAATG CCTGGTGTTG GCTGGATTTC 4080

GTGATTGTCA TGCTATCGCT TATAAATTTG GTTGCCGTTT GGTCGGGCTT AAATGATATA 4140

GCCGTGTTTA GATCAATGCG CACACTGCGC GCCCTAAGGC CATTGCGTGC TGTCTCTAGA 4200

TGGGAGGGTA TGAAAGTTGT CGTGAATGCG CTGGTTCAAG CTATACCGTC CATCTTCAAT 4260

GTGCTATTGG TGTGTCTGAT ATTTTGGCTT ATTTTTGCCA TTATGGGAGT ACAGCTTTTT 4320

GCTGGAAAAT ATTTTAAGTG TAAAGATGGT AATGACACTG TGCTGAGCCA TGAAATCATA 4380

CCGAATCGTA ATGCCTGCAA AAGTGAAAAC TACACCTGGG AAAATTCGGC AATGAACTTC 4440

GATCATGTAG GTAATGCGTA TCTCTGTCTA TTTCAAGTGG CCACCTTTAA GGGCTGGATC 4500

CAGATTATGA ACGATGCCAT TGATTCACGA GAGGTGGACA AGCAGCCGAT CCGAGAAACC 4560

AATATCTACA TGTATTTATA TTTCGTATTC TTCATTATAT TTGGATCATT TTTCACACTC 4620

AATCTGTTCA TTGGTGTTAT CATTGATAAT TTTAATGAAC AAAAGAAGAA AGCAGGTGGA 4680

TCATTAGAAA TGTTCATGAC AGAAGATCAG AAAAAGTACT ATAATGCTAT GAAAAAGATG 4740

GGCTCTAAAA AACCATTAAA AGCCATTCCA AGACCGAGGT GGCGACCACA AGCAATAGTA 4800

TTCGAAATAG TTACAGATAA AAAATTCGAT ATAATCATTA TGTTGTTCAT TGGCTTAAAC 4860

ATGTTTACCA TGACCCTCGA TCGGTACGAC GCCTCCGAGG CGTACAACAA TGTCCTCGAC 4920

AAACTCAATG GGATATTCGT AGTTATTTTC AGTGGCGAAT GTCTATTAAA AATATTCGCT 4980

TTACGATATC ACTATTTCAA AGAGCCATGG AATTTATTTG ATGTAGTAGT TGTCATTTTA 5040

TCCATCTTAG GTCTTGTACT CAGCGACATC ATTGAGAAGT ATTTCGTATC GCCGACACTG 5100

CTCCGTGTGG TGAGAGTGGC CAAAGTGGGT CGTGTCCTGC GTTTAGTCAA GGGTGCCAAG 5160

GGTATCCGGA CGTTGCTGTT CGCGTTAGCC ATGTCGTTGC CTGCCTTATT CAACATTTGT 5220

CTGTTGCTGT TCTTGGTGAT GTTCATCTTT GCTATCTTTG GCATGTCCTT CTTCATGCAT 5280

GTCAAAGAGA AGAGCGGCAT AAATGCTGTG TATAATTTTA AGACATTTGG CCAAAGTATG 5340

ATATTGCTGT TTCAGATGTC TACCTCAGCC GGTTGGGATG GTGTGTTAGA TGCCATTATC 5400

AATGAGGAAG ATTGCGATCC ACCCGACAAC GACAAGGGCT ATCCGGGCAA TTGTGGTTCA 5460

GCGACTGTTG GAATTACGTT TCTCCTTTCA TATCTAGTTA TAAGCTTTTT GATAGTTATT 5520

AATATGTACA TTGCTGTCAT TCTCGAGAAC TATAGCCAGG CTACGGAGGA TGTACAGGAG 5580

GGTCTCACCG ACGACGACTA TGATATGTAC TACGAGATTT GGCAACAATT CGATCCGGAG 5640

GGTACCCAGT ACATAAGATA CGACCAGCTG TCCGAGTTCC TGGACGTGCT GGAGCCGCCG 5700

CTGCAGATCC ACAAGCCGAA CAAGTACAAA ATCATATCGA TGGACATGCC GATATGTCGG 5760

GGCGACATGA TGTACTGTGT GGATATATTG GATGCCCTGA CCAAGGACTT CTTTGCGCGC 5820

AAGGGTAATC CGATCGAGGA GACGGGTGAA ATTGGTGAGA TTGCGGCGCG ACCGGACACC 5880

GAGGGCTATG ATCCGGTGTC GTCGACACTG TGGCGCCAGC GTGAGGAGTA CTGCGCCAAG 5940

CTGATACAGA ATGCGTGGCG GCGTTACAAG AATGGCCCAC CCCAGGAGGG TGATGAGGGC 6000

GAGGCGGCTG GTGGCGAAGA TGGTGCTGAA GGCGGTGAGG GTGAAGGCGG CAGCGGCGGC 6060

GGCGGCGATG ATGATGGTGG CTCAGCGACG GCGGCGGGAG CCACATCACC CACAGATCCA 6120

GATGCCGGCG AAGCAGATGG TGCCAGCGCC GGCAATGGTG GCGGCCCCCT TAGTCCGGGC 6180

TGTGTTAGTG GCGGCAGTAA TGGCCGCCAA ACGGCCGTAC TGGTCGAAAG CGATGGTTTT 6240

GTTACAAAAA ACGGTCATAA GGTTGTAATA CACTCGAGAT CGCCGAGCAT AACATCCAGG 6300

ACGGCAGATG TCTGA 6315

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2105 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Thr Glu Asp Ser Asp Ser Ile Ser Glu Glu Glu Arg Ser Leu Phe
1 5 10 15

Arg Pro Phe Thr Arg Glu Ser Leu Leu Gln Ile Glu Gln Arg Ile Ala
20 25 30

Glu His Glu Lys Gln Lys Glu Leu Glu Arg Lys Arg Ala Ala Glu Gly
35 40 45

Glu Gln Ile Arg Tyr Asp Asp Glu Asp Glu Asp Glu Gly Pro Gln Pro
50 55 60

Asp Pro Thr Leu Glu Gln Gly Val Pro Ile Pro Val Arg Met Gln Gly
65 70 75 80

Ser Phe Pro Pro Glu Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro
85 90 95

Phe Tyr Ser Asn Val Leu Thr Phe Val Val Ile Ser Lys Gly Lys Asp
100 105 110

Ile Phe Arg Phe Ser Ala Ser Lys Ala Met Trp Leu Leu Asp Pro Phe
115 120 125

Asn Pro Ile Arg Arg Val Ala Ile Tyr Ile Leu Val His Pro Leu Phe
130 135 140

Ser Leu Phe Ile Ile Thr Thr Ile Leu Thr Asn Cys Ile Leu Met Ile
145 150 155 160

Met Pro Thr Thr Pro Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly
165 170 175

Ile Tyr Thr Phe Glu Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile
180 185 190

Leu Cys Pro Phe Thr Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe
195 200 205

Val Val Ile Ala Leu Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn
210 215 220

Leu Ala Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val
225 230 235 240

Ala Ile Val Pro Gly Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser
245 250 255

Val Lys Asn Leu Arg Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser
260 265 270

Val Phe Ala Leu Met Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Gln
275 280 285

Lys Cys Ile Lys Arg Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr
290 295 300

Asp Glu Asn Trp Phe Leu His Asn Ser Asn Ser Ser Asn Trp Phe Thr
305 310 315 320

Glu Asn Asp Gly Glu Ser Tyr Pro Val Cys Gly Asn Val Ser Gly Ala
325 330 335

Gly Gln Cys Gly Glu Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn
340 345 350

Pro Asn Tyr Asp Tyr Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu
355 360 365

Ser Ala Phe Arg Leu Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln
370 375 380

His Val Leu Gln Ala Ala Gly Pro Trp His Met Leu Phe Phe Ile Val
385 390 395 400

Ile Ile Phe Leu Gly Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile
405 410 415

Val Ala Met Ser Tyr Asp Glu Leu Gln Lys Lys Ala Glu Glu Glu Glu
420 425 430

Ala Ala Glu Glu Glu Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala
435 440 445

Lys Ala Ala Lys Leu Glu Glu Arg Ala Asn Val Ala Ala Gln Ala Ala
450 455 460

Gln Asp Ala Ala Asp Ala Ala Ala Ala Ala Leu His Pro Glu Met Ala
465 470 475 480

Lys Ser Pro Thr Tyr Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly
485 490 495

Glu Lys Gly Asn Asp Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser
500 505 510

Val Glu Val Glu Ser Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala
515 520 525

Pro Thr Thr Ala Pro Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser
530 535 540

Leu Ser Leu Pro Gly Ser Pro Phe Asn Leu Arg Arg Gly Ser Arg Ser
545 550 555 560

Ser His Lys Tyr Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro
565 570 575

Gly Ser Asp Arg Lys Pro Leu Val Leu Gln Thr Tyr Gln Asp Ala Gln
580 585 590

Gln His Leu Pro Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser
595 600 605

Glu Glu Asn Gly Ala Ile Ile Val Pro Ala Tyr Tyr Cys Asn Leu Gly
610 615 620

Ser Arg His Ser Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr
625 630 635 640

Ser His Gly Asp Leu Leu Gly Gly Met Ala Ala Met Gly Ala Ser Thr
645 650 655

Met Thr Lys Glu Ser Lys Leu Arg Ser Arg Asn Thr Arg Asn Gln Ser
660 665 670

Ile Gly Ala Ala Thr Asn Gly Gly Ser Ser Thr Ala Gly Gly Gly Tyr
675 680 685

Pro Asp Ala Asn His Lys Glu Gln Arg Asp Tyr Glu Met Gly Gln Asp
690 695 700

Tyr Thr Asp Glu Ala Gly Lys Ile Lys His His Asp Asn Pro Phe Ile
705 710 715 720

Glu Pro Val Gln Thr Gln Thr Val Val Asp Met Lys Asp Val Met Val
725 730 735

Leu Asn Asp Ile Ile Glu Gln Ala Ala Gly Arg His Ser Arg Ala Ser
740 745 750

Glu Arg Gly Glu Asp Asp Asp Glu Asp Gly Pro Thr Phe Lys Asp Ile
755 760 765

Ala Leu Glu Tyr Ile Leu Lys Gly Ile Glu Ile Phe Cys Val Trp Asp
770 775 780

Cys Cys Trp Val Trp Leu Lys Phe Gln Glu Trp Val Ser Phe Ile Val
785 790 795 800

Phe Asp Pro Phe Val Glu Leu Phe Ile Thr Leu Cys Ile Val Val Asn
805 810 815

Thr Met Phe Met Ala Met Asp His His Asp Met Asn Pro Glu Leu Glu
820 825 830

Lys Val Leu Lys Ser Gly Asn Tyr Phe Phe Thr Ala Thr Phe Ala Ile
835 840 845

Glu Ala Ser Met Lys Leu Met Ala Met Ser Pro Lys Tyr Tyr Phe Gln
850 855 860

Glu Gly Trp Asn Ile Phe Asp Phe Ile Ile Val Ala Leu Ser Leu Leu
865 870 875 880

Glu Leu Gly Leu Glu Gly Val Gln Gly Leu Ser Val Leu Arg Ser Phe
885 890 895

Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn
900 905 910

Leu Leu Ile Ser Ile Met Gly Arg Thr Met Gly Ala Leu Gly Asn Leu
915 920 925

Thr Phe Val Leu Cys Ile Ile Ile Phe Ile Phe Ala Val Met Gly Met
930 935 940

Gln Leu Phe Gly Lys Asn Tyr Ile Asp His Lys Asp Arg Phe Lys Asp
945 950 955 960

His Glu Leu Pro Arg Trp Asn Phe Thr Asp Phe Met His Ser Phe Met
965 970 975

Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Ser Met Trp Asp
980 985 990

Cys Met Tyr Val Gly Asp Val Ser Cys Ile Pro Phe Phe Leu Ala Thr
995 1000 1005

Val Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu
1010 1015 1020

Leu Ser Asn Phe Gly Ser Ser Ser Leu Ser Ala Pro Thr Ala Asp Asn
1025 1030 1035 1040

Asp Thr Asn Lys Ile Ala Glu Ala Phe Asn Arg Ile Ala Arg Phe Lys
1045 1050 1055

Asn Trp Val Lys Arg Asn Ile Ala Asp Cys Phe Lys Leu Ile Arg Asn
1060 1065 1070

Lys Leu Thr Asn Gln Ile Ser Asp Gln Pro Ser Glu His Gly Asp Asn
1075 1080 1085

Glu Leu Glu Leu Gly His Asp Glu Ile Met Gly Asp Gly Leu Ile Lys
1090 1095 1100

Lys Gly Met Lys Gly Glu Thr Gln Leu Glu Val Ala Ile Gly Asp Gly
1105 1110 1115 1120

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Met Glu Phe Thr Ile His Gly Asp Met Lys Asn Asn Lys Pro Lys Lys
                1125                1130                1135

Ser Lys Phe Met Asn Asn Thr Thr Met Ile Gly Asn Ser Ile Asn His
            1140                1145                1150

Gln Asp Asn Arg Leu Glu His Glu Leu Asn His Arg Gly Leu Ser Ile
        1155                1160                1165

Gln Asp Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn
    1170                1175                1180

Arg Pro Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Ile Glu
1185                1190                1195                1200

Gly Glu Glu Lys Arg Asp Val Ser Lys Glu Asp Leu Gly Leu Asp Glu
                1205                1210                1215

Glu Leu Asp Glu Glu Ala Glu Gly Asp Glu Gly Gln Leu Asp Gly Asp
            1220                1225                1230

Ile Ile Ile His Ala Gln Asn Asp Asp Glu Ile Ile Asp Asp Tyr Pro
        1235                1240                1245

Ala Asp Cys Phe Pro Asp Ser Tyr Tyr Lys Lys Phe Pro Ile Leu Ala
    1250                1255                1260

Gly Asp Glu Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu
1265                1270                1275                1280

Lys Thr Phe Gln Leu Ile Glu Asn Lys Tyr Phe Glu Thr Ala Val Ile
                1285                1290                1295

Thr Met Ile Leu Met Ser Ser Leu Ala Leu Ala Leu Glu Asp Val His
            1300                1305                1310

Leu Pro Asp Arg Pro Val Met Gln Asp Ile Leu Tyr Tyr Met Asp Arg
        1315                1320                1325

Ile Phe Thr Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala
    1330                1335                1340

Leu Gly Phe Lys Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe
1345                1350                1355                1360

Val Ile Val Met Leu Ser Leu Ile Asn Leu Val Ala Val Trp Ser Gly
                1365                1370                1375
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Leu Asn Asp Ile Ala Val Phe Arg Ser Met Arg Thr Leu Arg Ala Leu
1380 1385 1390

Arg Pro Leu Arg Ala Val Ser Arg Trp Glu Gly Met Lys Val Val Val
1395 1400 1405

Asn Ala Leu Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val
1410 1415 1420

Cys Leu Ile Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe
1425 1430 1435 1440

Ala Gly Lys Tyr Phe Lys Cys Lys Asp Gly Asn Asp Thr Val Leu Ser
1445 1450 1455

His Glu Ile Ile Pro Asn Arg Asn Ala Cys Lys Ser Glu Asn Tyr Thr
1460 1465 1470

Trp Glu Asn Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu
1475 1480 1485

Cys Leu Phe Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn
1490 1495 1500

Asp Ala Ile Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr
1505 1510 1515 1520

Asn Ile Tyr Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser
1525 1530 1535

Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn
1540 1545 1550

Glu Gln Lys Lys Lys Ala Gly Gly Ser Leu Glu Met Phe Met Thr Glu
1555 1560 1565

Asp Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Met Gly Ser Lys Lys
1570 1575 1580

Pro Leu Lys Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val
1585 1590 1595 1600

Phe Glu Ile Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe
1605 1610 1615

Ile Gly Leu Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser
1620 1625 1630

Glu Ala Tyr Asn Asn Val Leu Asp Lys Leu Asn Gly Ile Phe Val Val
1635 1640 1645

Ile Phe Ser Gly Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His
1650 1655 1660

Tyr Phe Lys Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu
1665 1670 1675 1680

Ser Ile Leu Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val
1685 1690 1695

Ser Pro Thr Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val
1700 1705 1710

Leu Arg Leu Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala
1715 1720 1725

Leu Ala Met Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe
1730 1735 1740

Leu Val Met Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His
1745 1750 1755 1760

Val Lys Glu Lys Ser Gly Ile Asn Ala Val Tyr Asn Phe Lys Thr Phe
1765 1770 1775

Gly Gln Ser Met Ile Leu Leu Phe Gln Met Ser Thr Ser Ala Gly Trp
1780 1785 1790

Asp Gly Val Leu Asp Ala Ile Ile Asn Glu Glu Asp Cys Asp Pro Pro
1795 1800 1805

Asp Asn Asp Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly
1810 1815 1820

Ile Thr Phe Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile
1825 1830 1835 1840

Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu
1845 1850 1855

Asp Val Gln Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu
1860 1865 1870

Ile Trp Gln Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp
1875 1880 1885

Gln Leu Ser Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His
1890 1895 1900

Lys Pro Asn Lys Tyr Lys Ile Ile Ser Met Asp Met Pro Ile Cys Arg
1905 1910 1915 1920

Gly Asp Met Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp
1925 1930 1935

Phe Phe Ala Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly
1940 1945 1950

Glu Ile Ala Ala Arg Pro Asp Thr Glu Gly Tyr Asp Pro Val Ser Ser
1955 1960 1965

Thr Leu Trp Arg Gln Arg Glu Glu Tyr Cys Ala Lys Leu Ile Gln Asn
1970 1975 1980

Ala Trp Arg Arg Tyr Lys Asn Gly Pro Pro Gln Glu Gly Asp Glu Gly
1985 1990 1995 2000

Glu Ala Ala Gly Gly Glu Asp Gly Ala Glu Gly Gly Glu Gly Glu Gly
2005 2010 2015

Gly Ser Gly Gly Gly Gly Gly Asp Asp Gly Gly Ser Ala Thr Gly Ala
2020 2025 2030

Thr Ala Ala Ala Gly Ala Thr Ser Pro Ser Asp Pro Asp Ala Gly Glu
2035 2040 2045

Ala Asp Gly Ala Ser Val Gly Gly Pro Leu Ser Pro Gly Cys Val Ser
2050 2055 2060

Gly Gly Ser Asn Gly Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly
2065 2070 2075 2080

Phe Val Thr Lys Asn Gly His Lys Val Val Ile His Ser Arg Ser Pro
2085 2090 2095

Ser Ile Thr Ser Arg Thr Ala Asp Val
2100 2105

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2104 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Thr Glu Asp Ser Asp Ser Ile Ser Glu Glu Glu Arg Ser Leu Phe
1               5                   10                  15

Arg Pro Phe Thr Arg Glu Ser Leu Leu Gln Ile Glu Gln Arg Ile Ala
            20                  25                  30

Glu His Glu Lys Gln Lys Glu Leu Glu Arg Lys Arg Ala Ala Glu Gly
        35                  40                  45

Glu Gln Ile Arg Tyr Asp Asp Glu Asp Glu Asp Glu Gly Pro Gln Pro
    50                  55                  60

Asp Pro Thr Leu Glu Gln Gly Val Pro Ile Pro Val Arg Met Gln Gly
65                  70                  75                  80

Ser Phe Pro Pro Glu Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro
                85                  90                  95

Phe Tyr Ser Asn Val Leu Thr Phe Val Val Ile Ser Lys Gly Lys Asp
            100                 105                 110

Ile Phe Arg Phe Ser Ala Ser Lys Ala Met Trp Leu Leu Asp Pro Phe
        115                 120                 125

Asn Pro Ile Arg Arg Val Ala Ile Tyr Ile Leu Val His Pro Leu Phe
    130                 135                 140

Ser Leu Phe Ile Ile Thr Thr Ile Leu Thr Asn Cys Ile Leu Met Ile
145                 150                 155                 160

Met Pro Thr Thr Pro Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly
                165                 170                 175

Ile Tyr Thr Phe Glu Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile
            180                 185                 190

Leu Cys Pro Phe Thr Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe
        195                 200                 205
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Val Val Ile Ala Leu Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn
    210                 215                 220

Leu Ala Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val
225                 230                 235                 240

Ala Ile Val Pro Gly Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser
                245                 250                 255

Val Lys Asn Leu Arg Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser
            260                 265                 270

Val Phe Ala Leu Met Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Gln
        275                 280                 285

Lys Cys Ile Lys Arg Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr
    290                 295                 300

Asp Glu Asn Trp Phe Leu His Asn Ser Asn Ser Ser Asn Trp Phe Thr
305                 310                 315                 320

Glu Asn Asp Gly Glu Ser Tyr Pro Val Cys Gly Asn Val Ser Gly Ala
                325                 330                 335

Gly Gln Cys Gly Glu Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn
            340                 345                 350

Pro Asn Tyr Asp Tyr Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu
        355                 360                 365

Ser Ala Phe Arg Leu Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln
    370                 375                 380

His Val Leu Gln Ala Ala Gly Pro Trp His Met Leu Phe Phe Ile Val
385                 390                 395                 400

Ile Ile Phe Leu Gly Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile
                405                 410                 415

Val Ala Met Ser Tyr Asp Glu Leu Gln Lys Lys Ala Glu Glu Glu Glu
            420                 425                 430

Ala Ala Glu Glu Glu Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala
        435                 440                 445

Lys Ala Ala Lys Leu Glu Glu Arg Ala Asn Val Ala Ala Gln Ala Ala
    450                 455                 460
```

Gln Asp Ala Ala Asp Ala Ala Ala Ala Ala Leu His Pro Glu Met Ala
465 470 475 480

Lys Ser Pro Thr Tyr Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly
485 490 495

Glu Lys Gly Asn Asp Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser
500 505 510

Val Glu Val Glu Ser Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala
515 520 525

Pro Thr Thr Ala Pro Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser
530 535 540

Leu Ser Leu Pro Gly Ser Pro Phe Asn Leu Arg Arg Gly Ser Arg Ser
545 550 555 560

Ser His Lys Tyr Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro
565 570 575

Gly Ser Asp Arg Lys Pro Leu Val Leu Gln Thr Tyr Gln Asp Ala Gln
580 585 590

Gln His Leu Pro Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser
595 600 605

Glu Glu Asn Gly Ala Ile Ile Val Pro Ala Tyr Tyr Cys Asn Leu Gly
610 615 620

Ser Arg His Ser Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr
625 630 635 640

Ser His Gly Asp Leu Leu Gly Gly Met Ala Ala Met Gly Ala Ser Thr
645 650 655

Met Thr Lys Glu Ser Lys Leu Arg Ser Arg Asn Thr Arg Asn Gln Ser
660 665 670

Ile Gly Ala Ala Thr Asn Gly Gly Ser Ser Thr Ala Gly Gly Gly Tyr
675 680 685

Pro Asp Ala Asn His Lys Glu Gln Arg Asp Tyr Glu Met Gly Gln Asp
690 695 700

Tyr Thr Asp Glu Ala Gly Lys Ile Lys His His Asp Asn Pro Phe Ile
705 710 715 720

Glu Pro Val Gln Thr Gln Thr Val Val Asp Met Lys Asp Val Met Val
725 730 735

Leu Asn Asp Ile Ile Glu Gln Ala Ala Gly Arg His Ser Arg Ala Ser
740 745 750

Glu Arg Gly Glu Asp Asp Asp Glu Asp Gly Pro Thr Phe Lys Asp Ile
755 760 765

Ala Leu Glu Tyr Ile Leu Lys Gly Ile Glu Ile Phe Cys Val Trp Asp
770 775 780

Cys Cys Trp Val Trp Leu Lys Phe Gln Glu Trp Val Ser Phe Ile Val
785 790 795 800

Phe Asp Pro Phe Val Glu Leu Phe Ile Thr Leu Cys Ile Val Val Asn
805 810 815

Thr Met Phe Met Ala Met Asp His His Asp Met Asn Pro Glu Leu Glu
820 825 830

Lys Val Leu Lys Ser Gly Asn Tyr Phe Phe Thr Ala Thr Phe Ala Ile
835 840 845

Glu Ala Ser Met Lys Leu Met Ala Met Ser Pro Lys Tyr Tyr Phe Gln
850 855 860

Glu Gly Trp Asn Ile Phe Asp Phe Ile Ile Val Ala Leu Ser Leu Leu
865 870 875 880

Glu Leu Gly Leu Glu Gly Val Gln Gly Leu Ser Val Leu Arg Ser Phe
885 890 895

Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn
900 905 910

Leu Leu Ile Ser Ile Met Gly Arg Thr Met Gly Ala Leu Gly Asn Leu
915 920 925

Thr Phe Val Leu Cys Ile Ile Ile Phe Ile Phe Ala Val Met Gly Met
930 935 940

Gln Leu Phe Gly Lys Asn Tyr Ile Asp His Lys Asp Arg Phe Lys Asp
945 950 955 960

His Glu Leu Pro Arg Trp Asn Phe Thr Asp Phe Met His Ser Phe Met
965 970 975

Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Ser Met Trp Asp
980 985 990

Cys Met Tyr Val Gly Asp Val Ser Cys Ile Pro Phe Phe Leu Ala Thr
995 1000 1005

Val Val Ile Gly Asn Phe Val Val Leu Asn Leu Phe Leu Ala Leu Leu
1010 1015 1020

Leu Ser Asn Phe Gly Ser Ser Ser Leu Ser Ala Pro Thr Ala Asp Asn
1025 1030 1035 1040

Asp Thr Asn Lys Ile Ala Glu Ala Phe Asn Arg Ile Ala Arg Phe Lys
1045 1050 1055

Asn Trp Val Lys Arg Asn Ile Ala Asp Cys Phe Lys Leu Ile Arg Asn
1060 1065 1070

Lys Leu Thr Asn Gln Ile Ser Asp Gln Pro Ser Glu His Gly Asp Asn
1075 1080 1085

Glu Leu Glu Leu Gly His Asp Glu Ile Met Gly Asp Gly Leu Ile Lys
1090 1095 1100

Lys Gly Met Lys Gly Glu Thr Gln Leu Glu Val Ala Ile Gly Asp Gly
1105 1110 1115 1120

Met Glu Phe Thr Ile His Gly Asp Met Lys Asn Asn Lys Pro Lys Lys
1125 1130 1135

Ser Lys Phe Ile Asn Asn Thr Thr Met Ile Gly Asn Ser Ile Asn His
1140 1145 1150

Gln Asp Asn Arg Leu Glu His Glu Leu Asn His Arg Gly Leu Ser Ile
1155 1160 1165

Gln Asp Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn
1170 1175 1180

Arg Pro Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Ile Glu
1185 1190 1195 1200

Gly Glu Glu Lys Arg Asp Val Ser Lys Glu Asp Leu Gly Leu Asp Glu
1205 1210 1215

Glu Leu Asp Glu Glu Ala Glu Gly Asp Glu Gly Gln Leu Asp Gly Asp
1220 1225 1230

Ile Ile Ile His Ala Gln Asn Asp Asp Glu Ile Ile Asp Asp Tyr Pro
1235 1240 1245

Ala Asp Cys Phe Pro Asp Ser Tyr Tyr Lys Lys Phe Pro Ile Leu Ala
1250 1255 1260

Gly Asp Glu Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu
1265 1270 1275 1280

Lys Thr Phe Gln Leu Ile Glu Asn Lys Tyr Phe Glu Thr Ala Val Ile
1285 1290 1295

Thr Met Ile Leu Met Ser Ser Leu Ala Leu Ala Leu Glu Asp Val His
1300 1305 1310

Leu Pro Asp Arg Pro Val Met Gln Asp Ile Leu Tyr Tyr Met Asp Arg
1315 1320 1325

Ile Phe Thr Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala
1330 1335 1340

Leu Gly Phe Lys Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe
1345 1350 1355 1360

Val Ile Val Met Leu Ser Leu Ile Asn Leu Val Ala Val Trp Ser Gly
1365 1370 1375

Leu Asn Asp Ile Ala Val Phe Arg Ser Met Arg Thr Leu Arg Ala Leu
1380 1385 1390

Arg Pro Leu Arg Ala Val Ser Arg Trp Glu Gly Met Lys Val Val Val
1395 1400 1405

Asn Ala Leu Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val
1410 1415 1420

Cys Leu Ile Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe
1425 1430 1435 1440

Ala Gly Lys Tyr Phe Lys Cys Lys Asp Gly Asn Asp Thr Val Leu Ser
1445 1450 1455

His Glu Ile Ile Pro Asn Arg Asn Ala Cys Lys Ser Glu Asn Tyr Thr
1460 1465 1470

Trp Glu Asn Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu
1475 1480 1485

Cys Leu Phe Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn
1490 1495 1500

Asp Ala Ile Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr
1505 1510 1515 1520

Asn Ile Tyr Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser
1525 1530 1535

Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn
1540 1545 1550

Glu Gln Lys Lys Lys Ala Gly Gly Ser Leu Glu Met Phe Met Thr Glu
1555 1560 1565

Asp Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Met Gly Ser Lys Lys
1570 1575 1580

Pro Leu Lys Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val
1585 1590 1595 1600

Phe Glu Ile Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe
1605 1610 1615

Ile Gly Leu Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser
1620 1625 1630

Glu Ala Tyr Asn Asn Val Leu Asp Lys Leu Asn Gly Ile Phe Val Val
1635 1640 1645

Ile Phe Ser Gly Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His
1650 1655 1660

Tyr Phe Lys Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu
1665 1670 1675 1680

Ser Ile Leu Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val
1685 1690 1695

Ser Pro Thr Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val
1700 1705 1710

Leu Arg Leu Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala
1715 1720 1725

Leu Ala Met Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe
1730 1735 1740

Leu Val Met Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His
1745   1750   1755   1760

Val Lys Glu Lys Ser Gly Ile Asn Ala Val Tyr Asn Phe Lys Thr Phe
                1765   1770   1775

Gly Gln Ser Met Ile Leu Leu Phe Gln Met Ser Thr Ser Ala Gly Trp
            1780   1785   1790

Asp Gly Val Leu Asp Ala Ile Ile Asn Glu Glu Asp Cys Asp Pro Pro
        1795   1800   1805

Asp Asn Asp Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly
    1810   1815   1820

Ile Thr Phe Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile
1825   1830   1835   1840

Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu
                1845   1850   1855

Asp Val Gln Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu
            1860   1865   1870

Ile Trp Gln Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp
        1875   1880   1885

Gln Leu Ser Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His
    1890   1895   1900

Lys Pro Asn Lys Tyr Lys Ile Ile Ser Met Asp Met Pro Ile Cys Arg
1905   1910   1915   1920

Gly Asp Met Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp
                1925   1930   1935

Phe Phe Ala Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly
            1940   1945   1950

Glu Ile Ala Ala Arg Pro Asp Thr Glu Gly Tyr Asp Pro Val Ser Ser
        1955   1960   1965

Thr Leu Trp Arg Gln Arg Glu Glu Tyr Cys Ala Lys Leu Ile Gln Asn
    1970   1975   1980

Ala Trp Arg Arg Tyr Lys Asn Gly Pro Pro Gln Glu Gly Asp Glu Gly
1985   1990   1995   2000

Glu Ala Ala Gly Gly Glu Asp Gly Ala Glu Gly Gly Glu Gly Glu Gly
2005 2010 2015

Gly Ser Gly Gly Gly Gly Asp Asp Asp Gly Gly Ser Ala Thr Ala Ala
2020 2025 2030

Gly Ala Thr Ser Pro Thr Asp Pro Asp Ala Gly Glu Ala Asp Gly Ala
2035 2040 2045

Ser Ala Gly Asn Gly Gly Gly Pro Leu Ser Pro Gly Cys Val Ser Gly
2050 2055 2060

Gly Ser Asn Gly Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly Phe
2065 2070 2075 2080

Val Thr Lys Asn Gly His Lys Val Val Ile His Ser Arg Ser Pro Ser
2085 2090 2095

Ile Thr Ser Arg Thr Ala Asp Val
2100

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CGGTTGGGCT TTCCTGTC 18

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGGAATTCRA ADATRTTCCA NCCYTC 26

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCCGARGAYA THGAYCYNTA YTA 23

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CGTATCGCCT CCTCCTCG 18

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGTCTAGAT HTTYGCNATH TTYGGNATG 29

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GGGGAATTCN GGRTCRAAYT GYTGCCA 27

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGGTCTAGAR GANCARAARA ARTAYTA 27

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TCATACTTTG GCCCAATGTC 20

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CCCGAATTAG AGAAGGTGCT G 21

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

ACTATTGCTT GTGGTCGCCA C 21

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CATCNTTRGC NGCNTAGACN ATGAC 25

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GATTGAATGG ATCGAGCAGC C 21

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CGTTTCTCCT TTCATATCTA G 21

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GGAGBGGBGG NCKBGGNCKN GCTCA 25

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2100 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Met Thr Glu Asp Ser Asp Ser Ile Ser Glu Glu Glu Arg Ser Leu Phe
1               5                   10                  15

Arg Pro Phe Thr Arg Glu Ser Leu Val Gln Ile Glu Gln Arg Ile Ala
            20                  25                  30

Ala Glu His Glu Lys Gln Lys Glu Leu Glu Arg Lys Arg Ala Glu Gly
        35                  40                  45

Glu Val Pro Arg Tyr Gly Arg Lys Lys Lys Gln Lys Glu Ile Arg Tyr
    50                  55                  60

Asp Asp Glu Asp Glu Asp Glu Gly Pro Gln Pro Asp Pro Thr Leu Glu
65                  70                  75                  80

Gln Gly Val Pro Ile Pro Val Arg Leu Gln Gly Ser Phe Pro Pro Glu
                85                  90                  95

Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro Tyr Tyr Ser Asn Val
            100                 105                 110

Leu Thr Phe Val Val Val Ser Lys Gly Lys Asp Ile Phe Arg Phe Ser
        115                 120                 125

Ala Ser Lys Ala Met Trp Met Leu Asp Pro Phe Asn Pro Ile Arg Arg
    130                 135                 140

Val Ala Ile Tyr Ile Leu Val His Pro Leu Phe Ser Leu Phe Ile Ile
145                 150                 155                 160

Thr Thr Ile Leu Val Asn Cys Ile Leu Met Ile Met Pro Thr Thr Pro
                165                 170                 175

Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly Ile Tyr Thr Phe Glu
            180                 185                 190

Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile Leu Cys Pro Phe Thr
        195                 200                 205

Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe Val Val Ile Ala Leu
    210                 215                 220

Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn Leu Ala Ala Leu Arg
225                 230                 235                 240
```

Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val Ala Ile Val Pro Gly
245 250 255

Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser Val Lys Asn Leu Arg
260 265 270

Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser Val Phe Ala Leu Met
275 280 285

Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Glu Lys Cys Ile Lys Lys
290 295 300

Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr Asp Glu Asn Trp Asp
305 310 315 320

Tyr His Asn Arg Asn Ser Ser Asn Trp Tyr Ser Glu Asp Glu Gly Ile
325 330 335

Ser Phe Pro Leu Cys Gly Asn Ile Ser Gly Ala Gly Gln Cys Asp Asp
340 345 350

Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn Pro Asn Tyr Gly Tyr
355 360 365

Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu Ser Ala Phe Arg Leu
370 375 380

Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln Leu Val Leu Arg Ala
385 390 395 400

Ala Gly Pro Trp His Met Leu Phe Phe Ile Val Ile Ile Phe Leu Gly
405 410 415

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile Val Ala Met Ser Tyr
420 425 430

Asp Glu Leu Gln Arg Lys Ala Glu Glu Glu Glu Ala Ala Glu Glu Glu
435 440 445

Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala Lys Ala Ala Lys Leu
450 455 460

Glu Glu Arg Ala Asn Ala Gln Ala Gln Ala Ala Ala Asp Ala Ala Ala
465 470 475 480

Ala Glu Glu Ala Ala Leu His Pro Glu Met Ala Lys Ser Pro Thr Tyr

485 490 495

Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly Glu Lys Gly Asn Asp
500 505 510

Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser Val Glu Val Glu Ser
515 520 525

Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala Pro Thr Thr Ala His
530 535 540

Gln Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser Leu Ser Leu Pro
545 550 555 560

Gly Ser Pro Phe Asn Ile Arg Arg Gly Ser Arg Ser Ser His Lys Tyr
565 570 575

Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro Gly Ser Asp Arg
580 585 590

Lys Pro Leu Val Leu Ser Thr Tyr Gln Asp Ala Gln Gln His Leu Pro
595 600 605

Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser Glu Glu Asn Gly
610 615 620

Ala Ile Ile Val Pro Val Tyr Tyr Gly Asn Leu Gly Ser Arg His Ser
625 630 635 640

Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr Ser His Gly Asp
645 650 655

Leu Leu Gly Gly Met Ala Val Met Gly Val Ser Thr Met Thr Lys Glu
660 665 670

Ser Lys Leu Arg Asn Arg Asn Thr Arg Asn Gln Ser Val Gly Ala Thr
675 680 685

Asn Gly Gly Thr Thr Cys Leu Asp Thr Asn His Lys Leu Asp His Arg
690 695 700

Asp Tyr Glu Ile Gly Leu Glu Cys Thr Asp Glu Ala Gly Lys Ile Lys
705 710 715 720

His His Asp Asn Pro Phe Ile Glu Pro Val Gln Thr Gln Thr Val Val
725 730 735

```
Asp Met Lys Asp Val Met Val Leu Asn Asp Ile Ile Glu Gln Ala Ala
            740                 745                 750

Gly Arg His Ser Arg Ala Ser Asp Arg Gly Glu Asp Asp Asp Glu Asp
        755                 760                 765

Gly Pro Thr Phe Lys Asp Lys Ala Leu Glu Val Ile Leu Lys Gly Ile
    770                 775                 780

Asp Val Phe Cys Val Trp Asp Cys Cys Trp Val Trp Leu Lys Phe Gln
785                 790                 795                 800

Glu Trp Val Ser Leu Ile Val Phe Asp Pro Phe Val Glu Leu Phe Ile
                805                 810                 815

Thr Leu Cys Ile Val Val Asn Thr Met Phe Met Ala Met Asp His His
            820                 825                 830

Asp Met Asn Lys Glu Met Glu Arg Val Leu Lys Ser Gly Asn Tyr Phe
        835                 840                 845

Phe Thr Ala Thr Phe Ala Ile Glu Ala Thr Met Lys Leu Met Ala Met
    850                 855                 860

Ser Pro Lys Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Phe Ile
865                 870                 875                 880

Ile Val Ala Leu Ser Leu Leu Glu Leu Gly Leu Glu Gly Val Gln Gly
                885                 890                 895

Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala
            900                 905                 910

Lys Ser Trp Pro Thr Leu Asn Leu Leu Ile Ser Ile Met Gly Arg Thr
        915                 920                 925

Met Gly Ala Leu Gly Asn Leu Thr Phe Val Leu Cys Ile Ile Ile Phe
    930                 935                 940

Ile Phe Ala Val Met Gly Met Gln Leu Phe Gly Lys Asn Tyr His Asp
945                 950                 955                 960

His Lys Asp Arg Phe Pro Asp Gly Asp Leu Pro Arg Trp Asn Phe Thr
                965                 970                 975

Asp Phe Met His Ser Phe Met Ile Val Phe Arg Val Leu Cys Gly Glu
            980                 985                 990
```

Trp Ile Glu Ser Met Trp Asp Cys Met Tyr Val Gly Asp Val Ser Cys
995 1000 1005

Ile Pro Phe Phe Leu Ala Thr Val Val Ile Gly Asn Leu Val Val Leu
1010 1015 1020

Asn Leu Phe Leu Ala Leu Leu Leu Ser Asn Phe Gly Ser Ser Ser Leu
1025 1030 1035 1040

Ser Ala Pro Thr Ala Asp Asn Asp Thr Asn Lys Ile Ala Glu Ala Phe
1045 1050 1055

Asn Arg Ile Gly Arg Phe Lys Ser Trp Val Lys Arg Asn Ile Ala Asp
1060 1065 1070

Cys Phe Lys Leu Ile Arg Asn Lys Leu Thr Asn Gln Ile Ser Asp Gln
1075 1080 1085

Pro Ser Glu His Gly Asp Asn Glu Leu Glu Leu Gly His Asp Glu Ile
1090 1095 1100

Leu Ala Asp Gly Leu Ile Lys Lys Gly Ile Lys Glu Gln Thr Gln Leu
1105 1110 1115 1120

Glu Val Ala Ile Gly Asp Gly Met Glu Phe Thr Ile His Gly Asp Met
1125 1130 1135

Lys Asn Asn Lys Pro Lys Lys Ser Lys Tyr Leu Asn Asn Ala Thr Asp
1140 1145 1150

Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn Arg Pro
1155 1160 1165

Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Met Glu Gly Glu
1170 1175 1180

Glu Lys Arg Asp Ala Ser Lys Glu Asp Leu Gly Leu Asp Glu Glu Leu
1185 1190 1195 1200

Asp Glu Glu Gly Glu Cys Glu Glu Gly Pro Leu Asp Gly Asp Ile Ile
1205 1210 1215

Ile His Ala His Asp Glu Asp Ile Leu Asp Glu Tyr Pro Ala Asp Cys
1220 1225 1230

Cys Pro Asp Ser Tyr Tyr Lys Lys Phe Pro Ile Leu Ala Gly Asp Asp
1235 1240 1245

Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu Lys Thr Phe
1250 1255 1260

Arg Leu Ile Glu Asp Lys Tyr Phe Glu Thr Ala Val Ile Thr Met Ile
1265 1270 1275 1280

Leu Met Ser Ser Leu Ala Leu Ala Leu Glu Asp Val His Leu Pro Gln
1285 1290 1295

Arg Pro Ile Leu Gln Asp Ile Leu Tyr Tyr Met Asp Arg Ile Phe Thr
1300 1305 1310

Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala Leu Gly Phe
1315 1320 1325

Lys Val Tyr Leu Thr Asn Ala Trp Cys Trp Leu Asp Phe Val Ile Val
1330 1335 1340

Met Val Ser Leu Ile Asn Phe Val Ala Ser Leu Val Gly Ala Gly Gly
1345 1350 1355 1360

Ile Gln Ala Phe Lys Thr Met Arg Thr Leu Arg Ala Leu Arg Pro Leu
1365 1370 1375

Arg Ala Met Ser Arg Met Gln Gly Met Arg Val Val Val Asn Ala Leu
1380 1385 1390

Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val Cys Leu Ile
1395 1400 1405

Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe Ala Gly Lys
1410 1415 1420

Tyr Phe Lys Cys Glu Asp Met Asn Gly Thr Lys Leu Ser His Glu Ile
1425 1430 1435 1440

Ile Pro Asn Arg Asn Ala Cys Glu Ser Glu Asn Tyr Thr Trp Val Asn
1445 1450 1455

Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu Cys Leu Phe
1460 1465 1470

Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn Asp Ala Ile
1475 1480 1485

Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr Asn Ile Tyr
1490 1495 1500

Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser Phe Phe Thr
1505 1510 1515 1520

Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Glu Gln Lys
1525 1530 1535

Lys Lys Ala Gly Gly Ser Leu Glu Met Phe Met Thr Glu Asp Gln Lys
1540 1545 1550

Lys Tyr Tyr Ser Ala Met Lys Lys Met Gly Ser Lys Lys Pro Leu Lys
1555 1560 1565

Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val Phe Glu Ile
1570 1575 1580

Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe Ile Gly Leu
1585 1590 1595 1600

Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser Asp Thr Tyr
1605 1610 1615

Asn Ala Val Leu Asp Tyr Leu Asn Ala Ile Phe Val Val Ile Phe Ser
1620 1625 1630

Ser Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His Tyr Phe Ile
1635 1640 1645

Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu Ser Ile Leu
1650 1655 1660

Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val Ser Pro Thr
1665 1670 1675 1680

Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val Leu Arg Leu
1685 1690 1695

Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Ala Met
1700 1705 1710

Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe Leu Val Met
1715 1720 1725

Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His Val Lys Glu
1730 1735 1740

Lys Ser Gly Ile Asn Asp Val Tyr Asn Phe Lys Thr Phe Gly Gln Ser
1745 1750 1755 1760

Met Ile Leu Leu Phe Gln Met Ser Thr Ser Ala Gly Trp Asp Gly Val
1765 1770 1775

Leu Asp Ala Ile Ile Asn Glu Glu Ala Cys Asp Pro Pro Asp Asn Asp
1780 1785 1790

Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly Ile Thr Phe
1795 1800 1805

Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile Asn Met Tyr
1810 1815 1820

Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu Asp Val Gln
1825 1830 1835 1840

Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu Ile Trp Gln
1845 1850 1855

Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp Gln Leu Ser
1860 1865 1870

Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His Lys Pro Asn
1875 1880 1885

Lys Tyr Lys Ile Ile Ser Met Asp Ile Pro Ile Cys Arg Gly Asp Leu
1890 1895 1900

Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp Phe Phe Ala
1905 1910 1915 1920

Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly Glu Ile Ala
1925 1930 1935

Ala Arg Pro Asp Thr Glu Gly Tyr Glu Pro Val Ser Ser Thr Leu Trp
1940 1945 1950

Arg Gln Arg Glu Glu Tyr Cys Ala Arg Leu Ile Gln His Ala Trp Arg
1955 1960 1965

Lys His Lys Ala Arg Gly Glu Gly Gly Gly Ser Phe Glu Pro Asp Thr
1970 1975 1980

Asp His Gly Asp Gly Gly Asp Pro Asp Ala Gly Asp Pro Ala Pro Asp
1985 1990 1995 2000

Glu Ala Thr Asp Gly Asp Ala Pro Ala Gly Gly Asp Gly Ser Val Asn
2005 2010 2015

Gly Thr Ala Glu Gly Ala Ala Asp Ala Asp Glu Ser Asn Val Asn Ser
2020 2025 2030

Pro Gly Glu Asp Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
2035 2040 2045

Ala Ala Gly Thr Thr Thr Ala Gly Ser Pro Gly Ala Gly Ser Ala Gly
2050 2055 2060

Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly Phe Val Thr Lys Asn
2065 2070 2075 2080

Gly His Lys Val Val Ile His Ser Arg Ser Pro Ser Ile Thr Ser Arg
2085 2090 2095

Thr Ala Asp Val
2100

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of *Musca domestica*, wherein said voltage-sensitive sodium channel is capable of conferring sensitivity or resistance to an insecticide in *Musca domestica*.

2. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid is deoxyribonucleic acid.

3. The isolated nucleic acid molecule of claim 2 wherein said deoxyribonucleic acid is cDNA.

4. The isolated nucleic acid molecule of claim 1 wherein said voltage-sensitive sodium channel confers susceptibility to an insecticide in *Musca domestica*.

5. The isolated nucleic acid molecule of claim 4 wherein said nucleic acid molecule has a nucleotide sequence as shown in SEQ ID NO:1.

6. The isolated nucleic acid molecule of claim 4 wherein said nucleic acid molecule encodes an amino acid sequence as shown in SEQ ID NO:3.

7. The isolated nucleic acid molecule of claim 1 wherein said voltage-sensitive sodium channel confers resistance to an insecticide in *Musca domestica*.

8. The isolated nucleic acid molecule of claim 7 wherein said nucleic acid molecule has a nucleotide sequence as shown in SEQ ID NO:2.

9. The isolated nucleic acid molecule of claim 7 wherein said nucleic acid molecule encodes an amino acid sequence as shown in SEQ ID NO:4.

10. The isolated nucleic acid molecule of claim 7 wherein said nucleic acid molecule has the nucleotide sequence of a second nucleic acid molecule with one or more mutations therein, wherein said second nucleic acid molecule encodes an insecticide sensitive voltage-sensitive sodium channel of *Musca domestica*, and wherein said one or more mutations in said second nucleic acid molecule render the resulting voltage-sensitive sodium channel resistant to an insecticide.

11. The isolated nucleic acid molecule of claim 10 wherein said nucleotide sequence of said second nucleic acid molecule encodes amino acid SEQ ID NO:3, and wherein said one or more mutations in said second nucleic acid molecule are selected from the group consisting of a substitution for amino acid residue 1014 of SEQ ID NO:3, a substitution for amino acid residue 1140 of SEQ ID NO:3, a substitution for amino acid residue 2023 of SEQ ID NO:3, a deletion of one or more of amino acid residues 2031-2034 of SEQ ID NO:3, a substitution for amino acid residue 2042 of SEQ ID NO:3, a substitution for amino acid residue 2054 of SEQ ID NO:3, and an insertion of one to three amino acid residues between amino acid residues 2055 and 2056 of SEQ ID NO:3.

12. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid is ribonucleic acid.

13. The isolated nucleic acid molecule of claim 12 wherein said ribonucleic acid is mRNA.

14. An antisense nucleic acid molecule complementary to at least a portion of the mRNA of claim 13.

15. An expression vector comprising the antisense nucleic acid molecule of claim 14.

16. The expression vector of claim 15 wherein the expression vector is a baculovirus.

17. A method of decreasing expression of a voltage-sensitive sodium channel in an insect, said method comprising infecting an insect with the baculovirus vector of claim 16, wherein infection of said insect by said baculovirus results in incorporation of said antisense nucleic acid molecule into the genome of said insect, thereby blocking expression of voltage-sensitive sodium channels in said insect cell.

18. A ribozyme having a recognition sequence complementary to a portion of the mRNA of claim 13.

19. An expression vector comprising the ribozyme of claim 18.

20. The expression vector of claim 19 wherein the expression vector is a baculovirus.

21. A method of decreasing expression of a voltage-sensitive sodium channel in an insect, said method comprising infecting an insect with the baculovirus vector of claim 20, wherein infection of said insect by said baculovirus results in expression of said ribozyme in said insect, thereby decreasing expression of voltage-sensitive sodium channels in said insect cell.

22. A cell comprising the nucleic acid molecule of claim 1.

23. The cell of claim 22 wherein the cell is a *Xenopus* oocyte.

24. The cell of claim 22 wherein the cell is an insect cell line.

25. The cell of claim 24 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

26. An expression vector comprising the nucleic acid molecule of claim 1.

27. The expression vector of claim 26 wherein said expression vector is selected from the group consisting of a plasmid and a virus.

28. A cell comprising the expression vector of claim 26.

29. The cell of claim 28 wherein the cell is a *Xenopus* oocyte.

30. The cell of claim 28 wherein the cell is an insect cell line.

31. The cell of claim 30 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

32. The isolated nucleic acid molecule of claim 1 wherein said insecticide is selected from the group consisting of DDT, DDT analogs, and pyrethroids.

33. A method of producing a voltage-sensitive sodium channel, said method comprising:

introducing the nucleic acid molecule of claim 1 into a cell; and

allowing said cell to express said nucleic acid molecule resulting in the production of a voltage-sensitive sodium channel in said cell.

34. The method of claim 33 wherein the cell is a *Xenopus* oocyte.

35. The method of claim 33 wherein the cell is an insect cell line.

36. The method of claim 35 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

37. A method of producing a voltage-sensitive sodium channel, said method comprising:

introducing the nucleic acid molecule of claim 1 and a second nucleic acid molecule encoding a tip E protein into a cell; and

allowing said cell to coexpress said nucleic acid molecule and said second nucleic acid molecule, resulting in the production of a voltage-sensitive sodium channel in said cell.

38. The method of claim 37 wherein the cell is a *Xenopus* oocyte.

39. The method of claim 37 wherein the cell is an insect cell line.

40. The method of claim 39 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

41. A method of screening a chemical agent for the ability of the chemical agent to modify sodium channel function, said method comprising:

introducing the nucleic acid molecule of claim 1 into a host cell;

expressing said voltage-sensitive sodium channel encoded by said nucleic acid molecule in the host cell so as to result in the functional expression of a voltage-sensitive sodium channel in the host cell;

exposing the cell to a chemical agent; and

evaluating the exposed cell to determine if the chemical agent modifies the function of the voltage-sensitive sodium channel.

42. The method of claim 41 wherein the cell is a *Xenopus* oocyte.

43. The method of claim 41 wherein the cell is an insect cell line.

44. The method of claim 43 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

45. The method of claim 41 wherein said evaluation comprises monitoring sodium transport through said voltage-sensitive sodium channel.

46. The method of claim 41 wherein said evaluation comprises monitoring quanidinium transport through said voltage-sensitive sodium channel.

47. A method of screening a chemical agent for the ability of the chemical agent to modify sodium channel function, said method comprising:

introducing the nucleic acid molecule of claim 1 and a second nucleic acid molecule encoding a tip E protein into a host cell;

allowing said host cell to coexpress said nucleic acid molecule and said second nucleic acid molecule so as to result in the functional expression of a voltage-sensitive sodium channel in the host cell;

exposing the cell to a chemical agent; and

evaluating the exposed cell to determine if the chemical agent modifies the function of the voltage-sensitive sodium channel.

48. The method of claim 47 wherein the cell is a *Xenopus* oocyte.

49. The method of claim 47 wherein the cell is an insect cell line.

50. The method of claim 49 wherein said insect cell line is selected from the group consisting of a *Drosophila Schneider* cell line, a *Drosophila* K_c cell line, an Sf9 cell line, and a High Five® cell line.

51. The method of claim 47 wherein said evaluation comprises monitoring sodium transport through said voltage-sensitive sodium channel.

52. The method of claim 47 wherein said evaluation comprises monitoring quanidinium transport through said voltage-sensitive sodium channel.

53. A method of obtaining DNA encoding a voltage-sensitive sodium channel, said method comprising:

selecting a DNA molecule encoding a voltage-sensitive sodium channel of an insect, said DNA molecule having a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2;

designing an oligonucleotide probe for a voltage-sensitive sodium channel based on SEQ ID NO:1 or SEQ ID NO:2;

probing a genomic or cDNA library of an insect with the oligonucleotide probe; and

obtaining clones from said library that are recognized by said oligonucleotide probe, so as to obtain DNA encoding a voltage-sensitive sodium channel.

54. A method of obtaining DNA encoding a voltage-sensitive sodium channel, said method comprising:

selecting a DNA molecule encoding a voltage-sensitive sodium channel of an insect, said DNA molecule having a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2;

designing degenerate oligonucleotide primers based on SEQ ID NO:1 or SEQ ID NO:2; and

utilizing said oligonucleotide primers in a polymerase chain reaction on a DNA sample to identify homologous DNA encoding a voltage-sensitive sodium channel in said sample.

55. An isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of an insect, said nucleic acid molecule encoding a first amino acid sequence

having at least 95% amino acid identity to a second amino acid sequence, said second amino acid sequence being as shown in SEQ ID NO:3.

56. An isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of an insect, said nucleic acid molecule encoding a first amino acid sequence having at least 95% amino acid identity to a second amino acid sequence, said second amino acid sequence being as shown in SEQ ID NO:4.

57. An isolated voltage-sensitive sodium channel of *Musca domestica*, wherein said voltage-sensitive sodium channel is capable of conferring sensitivity or resistance to an insecticide in *Musca domestica*.

58. The voltage-sensitive sodium channel of claim 57 wherein said voltage-sensitive sodium channel confers susceptibility to an insecticide in *Musca domestica*.

59. The voltage-sensitive sodium channel of claim 58 wherein said voltage-sensitive sodium channel is encoded by a nucleotide sequence as shown in SEQ ID NO:1.

60. The voltage-sensitive sodium channel of claim 58 wherein said voltage-sensitive sodium channel is comprised of a protein having an amino acid sequence as shown in SEQ ID NO:3.

61. The voltage-sensitive sodium channel of claim 57 wherein said voltage-sensitive sodium channel confers resistance to an insecticide in *Musca domestica*.

62. The voltage-sensitive sodium channel of claim 61 wherein said voltage-sensitive sodium channel is encoded by a nucleotide sequence as shown in SEQ ID NO:2.

63. The voltage-sensitive sodium channel of claim 61 wherein said voltage-sensitive sodium channel is comprised of a protein having an amino acid sequence as shown in SEQ ID NO:4.

64. The voltage-sensitive sodium channel of claim 61 wherein said voltage-sensitive sodium channel is encoded by a nucleic acid molecule having the nucleotide sequence of a second nucleic acid molecule with one or more mutations therein, wherein said second nucleic acid molecule encodes an insecticide sensitive voltage-sensitive sodium channel of *Musca domestica*, and wherein said one or more mutations in said second nucleic acid molecule render the resulting voltage-sensitive sodium channel resistant to an insecticide.

65. The voltage-sensitive sodium channel of claim 64 wherein said nucleotide sequence of said second nucleic acid molecule encodes amino acid SEQ ID NO:3, and wherein said one or more mutations in said second nucleic acid molecule are selected from the group consisting of a substitution for amino acid residue 1014 of SEQ ID NO:3, a substitution for amino acid residue 1140 of SEQ ID NO:3, a substitution for amino acid residue 2023 of SEQ ID NO:3, a deletion of one or more of amino acid residues 2031-2034 of SEQ ID NO:3, a substitution for amino acid residue 2042 of SEQ ID NO:3, a substitution for amino acid residue 2054 of SEQ ID NO:3, and an insertion of one to three amino acid residues between amino acid residues 2055 and 2056 of SEQ ID NO:3.

66. The voltage-sensitive sodium channel of claim 57 wherein said insecticide is selected from the group consisting of DDT, DDT analogs, and pyrethroids.

67. An antibody or fragment thereof specific for the voltage-sensitive sodium channel of claim 57.

68. The antibody of claim 67 wherein said antibody comprises a monoclonal antibody.

69. The antibody of claim 67 wherein said antibody comprises a polyclonal antibody.

70. A method of detecting presence of a voltage-sensitive sodium channel in a sample, said method comprising:

contacting a sample with the antibody or fragment thereof of claim 67, wherein said antibody or fragment thereof binds to any of said voltage-sensitive sodium channel present in said sample, forming a complex therewith; and

detecting said complex, thereby detecting presence of a voltage-sensitive sodium channel in said sample.

71. An isolated voltage-sensitive sodium channel of *Musca domestica*, wherein the voltage-sensitive sodium channel is comprised of a protein having a first amino acid sequence with at least 95% amino acid identity to a second amino acid sequence, said second amino acid sequence being as shown in SEQ ID NO:3.

72. An isolated voltage-sensitive sodium channel of *Musca domestica*, wherein the voltage-sensitive sodium channel is comprised of a protein having a first amino acid sequence with at least 95% amino acid identity to a

second amino acid sequence, said second amino acid sequence being as shown in SEQ ID NO:4.

73. A plasmid designated pPJI1 and deposited with the American Type Culture Collection under Accession No. __________.

74. A KpnI/AatII restriction fragment of the plasmid designated pPJI1 of claim 73, said restriction fragment being about 3620 bp.

75. A plasmid designated pPJI2 and deposited with the American Type Culture Collection under Accession No. __________.

76. An AatII/SphII restriction fragment of the plasmid designated pPJI2 of claim 75, said restriction fragment being about 2700 bp.

77. An isolated nucleic acid molecule consisting of a KpnI/AatII restriction fragment of about 3620 bp of the plasmid designated pPJI1 ligated at the AatII site to the AatII site of an AatII/SphII restriction fragment of about 2700 bp of the plasmid designated pPJI2.

INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES

ABSTRACT OF THE DISCLOSURE

The present invention is directed to isolated nucleic acid molecules encoding a voltage-sensitive sodium channel (VSSC) of *Musca domestica*, the VSSC being capable of conferring insecticide susceptibility or insecticide resistance to *Musca domestica*, as well as to the isolated voltage-sensitive sodium channels of *Musca domestica* encoded thereby. Nucleic acid molecules encoding insecticide susceptible VSSCs and nucleic acid molecules encoding insecticide resistant VSSCs are provided. Methods for increasing or decreasing the expression of functional voltage-sensitive sodium channels in host cells are also provided, as well as methods using the sodium channels. Also provided is a method for isolating other voltage-sensitive sodium channels.

PATENT
Docket No.: **19603/606 (CRF D-1657B)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) :	David M. Soderlund, Douglas C. Knipple, and Patricia J. Ingles	)	Examiner: To Be Assigned
Serial No. :	To Be Assigned (Division of Serial No. 08/772,512, filed December 24, 1996)	)	Art Unit: To Be Assigned
Filed :	Herewith	)	
For :	INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES	)	Batch No:

SUBMISSION OF FORMAL DRAWINGS

Assistant Commissioner for Patents
Washington, D.C. 20231
Box: Patent Application

Dear Sir:

Enclosed for filing in the subject application are 7 sheets of formal drawings.

Respectfully submitted,

Date: 10/28/99

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R347505.1

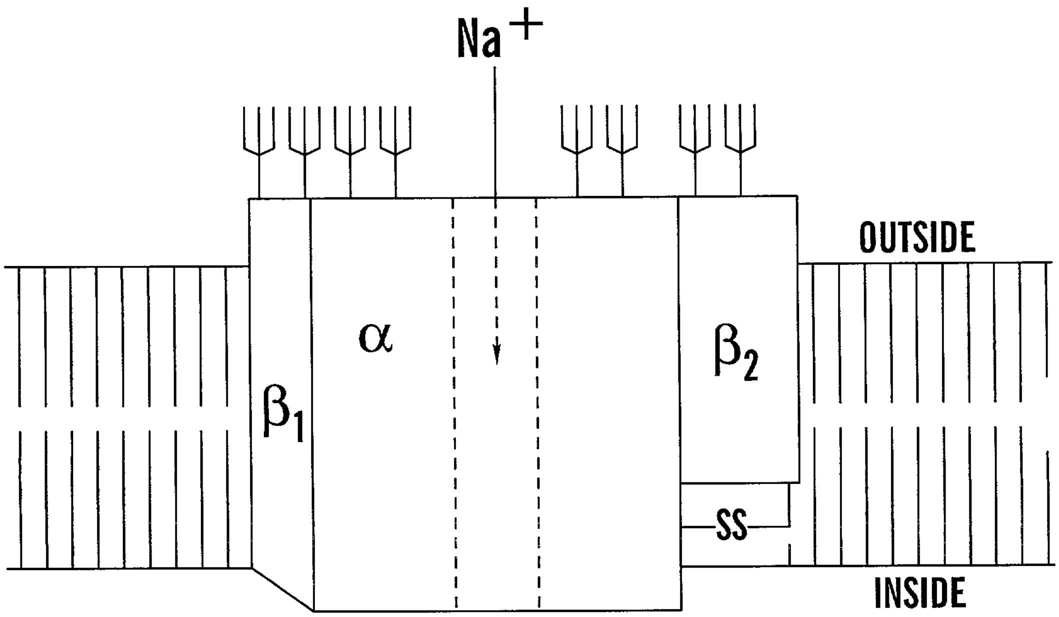

FIG. 1

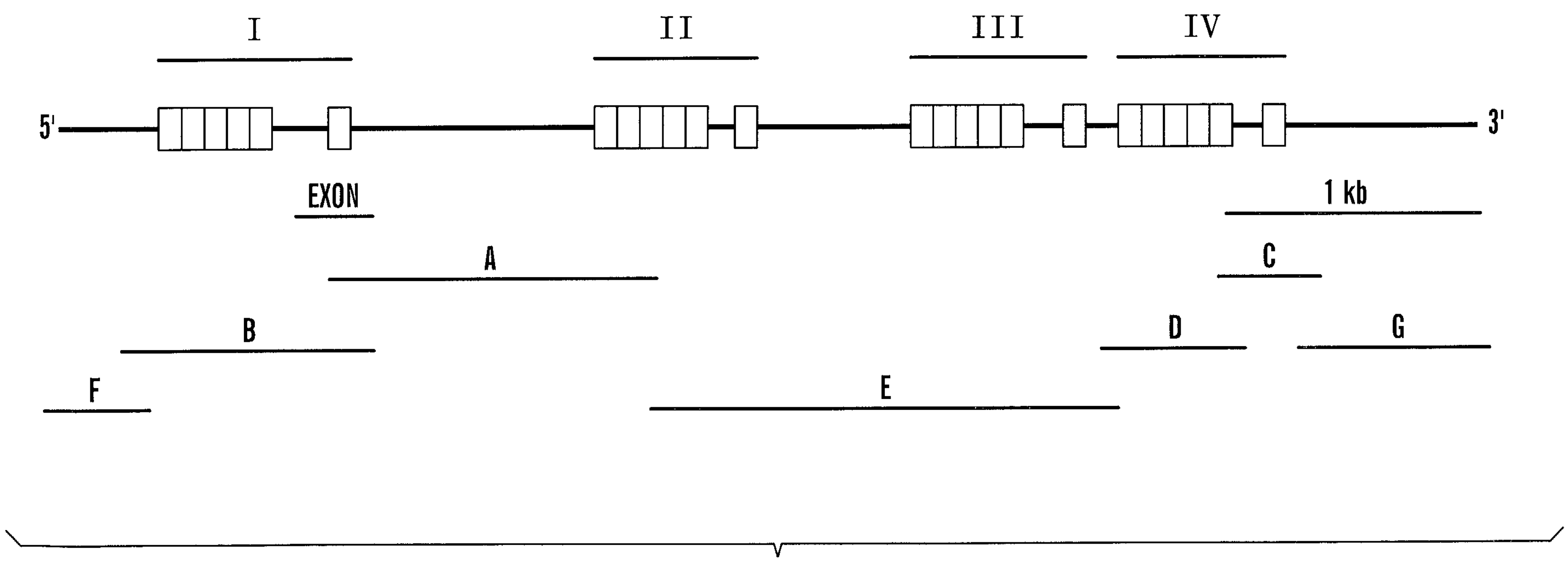

FIG. 2

3/7

```
NAIDM    MTEDSDSISEEERSLFRPFTRESLLQIEQRIA.EHEKQKELERKRAAEGE...........QIRYDDEDEDEGPQPDPTLEQGVPIPVRMQ 79
538ge    ------------------------L-------.------------A----...........Q---------------------------M- 79
para     ------------------------V-------A------------.----VPRYGRKKKQKE---------------------------L- 90

                                                                    IS1                         IS2
GSFPPELASTPLEDIDPFYSNVLTFVVISKGKDIFRFSASKAMWLLDPFNPIRRVAIYILVHPLFSLFIITTILTNCILMIMPTTPTVESTEVIFTGIYT 179
-----------------F---------I----------------L-----------------------------T------------------------- 179
-----------------Y---------V----------------M-----------------------------V------------------------- 190

                               IS3                     IS4                                      IS5
FESAVKVMARGFILCPFTYLRDAWNWLDFVVIALAYVTMGIDLGNLAALRTFRVLRALKTVAIVPGLKTIVGAVIESVKNLRDVIILTMFSLSVFALMGL 279
---------------------------------------------------------------------------------------------------- 279
---------------------------------------------------------------------------------------------------- 290

                      #           #                 #                                            IP
QIYMGVLTQKCIKRFPLDGSWGNLTDENWFLHNSNSSNWFTENDGESYPVCGNVSGAGQCGEDYVCLQGFGPNPNYDYTSFDSFGWAFLSAFRLMTQDFW 379
--------Q----R---------------FL--S-----FT-ND-E-Y-V---V------GE--------------D----------------------- 379
--------E----K---------------DY--R-----YS-DE-I-F-L---I------DD--------------G----------------------- 390

                         IS6
EDLYQHVLQAAGPWHMLFFIVIIFLGSFYLVNLILAIVAMSYDELQKKAEEEEAAEEEAIREAEEAAAAKAAKLEERANVAAQAAQDAADAAAAALHPEM 479
-----H--Q-------------------------------------K--------------------------------VA----Q---D-AA------- 479
-----L--R-------------------------------------R--------------------------------AQ----A---A-EE------- 490

                                                              *               *
AKSPTYSCISYELFVGGEKGNDDNNKEKMSIRSVEVESESVSVIQRQPAPTTAP.ATKVRKVSTTSLSLPGSPFNLRRGSRSSHKYTIRNGRGRFGIPGS 578
-----------------------------------------------------P.--------------------L------------------------ 578
-----------------------------------------------------HQ--------------------I------------------------ 590
```

FIG. 3A

```
                                                  *                                        #
DRKPLVLQTYQDAQQHLPYADDSNAVTPMSEENGAIIVPAYYCNLGSRHSSYTSHQSRISYTSHGDLLGGMAAMGASTMTKESKLRSRNTRNQSIGAATN 678
-------Q-------------------------------A--C-----------------------------A--A----------S-------I--ATN 678
-------S-------------------------------V--G-----------------------------V--V----------N-------V--TNG 690

GGSSTAGGGYPDANHK.EQRDYEMGQDYTDEAGKIKHHDNPFIEPVQTQTVVDMKDVMVLNDIIEQAAGRHSRASERGEDDDEDGPTFKDIALEYILKGI 777
-GSSTAGGGYP-A---.EQ----M-QDY-----------------------------------------------E--------------I---Y----- 777
-TTCL......-T---LDH----I-LEC-----------------------------------------------D--------------K---V----- 784
                              IIS1                              IIS2                          IIS3
EIFCVWDCCWVWLKFQEWVSFIVFDPFVELFITLCIVVNTMFMAMDHHDMNPELEKVLKSGNYFFTATFAIEASMKLMAMSPKYYFQEGWNIFDFIIVAL 877
EI------------------F------------------------------P-L-K-----------------S-------------------------- 877
DV------------------L------------------------------K-M-R-----------------T-------------------------- 884
                      IIS4                               IIS5                            #
SLLELGLEGVQGLSVLRSFRLLRVFKLAKSWPTLNLLISIMGRTMGALGNLTFVLCIIIFIFAVMGMQLFGKNYIDHKDRFKDHELPRWNFTDFMHSFMI 977
--------------------------------------------------------------------------I------K-HE--------------- 977
--------------------------------------------------------------------------H------P-GD--------------- 984
       IIP                      IIS6 ◆                        #
VFRVLCGEWIESMWDCMYVGDVSCIPFFLATVVIGNLVVLNLFLALLLSNFGSSSLSAPTADNDTNKIAEAFNRIARFKNWVKRNIADCFKLIRNKLTNQ 1077
------------------------------------F--------------------------------------A---N-------------------- 1077
------------------------------------L--------------------------------------G---S-------------------- 1084

                                                              ◆ #                        *
ISDQPSEHGDNELELGHDEIMGDGLIKKGMKGETQLEVAIGDGMEFTIHGDMKNNKPKKSKFMNNTTMIGNSINHQDNRLEHELNHRGLSIQDDDTASIN 1177
--------------------MG-------M-GE----------------------------FI--T-MIGNSINHQDNRLEHELNHRGLSIQ-------- 1177
--------------------LA-------I-EQ----------------------------YL--A-.........................-------- 1159
```

FIG. 3B

```
             •                *
SYGSHKNRPFKDESHKGSAETIEGEEKRDVSKEDLGLDEELDEEAEGDEGQLDGDIIIHAQNDDEIIDDYPADCFPDSYYKKFPILAGDEDSPFWQGWGN 1277
---------------------I-------V--------------A-GD--Q---------QN-DE-I-D-----F--------------E---------- 1277
---------------------M-------A--------------G-CE--P---------H.-ED-L-E-----C--------------D---------- 1258
                IIIS1                                  IIIS2                          IIIS3
LRLKTFQLIENKYFETAVITMILMSSLALALEDVHLPDRPVMQDILYYMDRIFTVIFFLEMLIKWLALGFKVYFTNAWCWLDFVIVMLSLINLVAVWSGL 1377
------Q---N--------------------------D--VM-------------------------------F-------------L----L--VWS-L 1377
------R---D--------------------------Q--IL-------------------------------L-------------V----F--SLV-A 1358
          IIIS4                                  IIIS5                   #                  #
NDIAVFRSMRTLRALRPLRAVSRWEGMKVVVNALVQAIPSIFNVLLVCLIFWLIFAIMGVQLFAGKYFKCKDGNDTVLSHEIIPNRNACKSENYTWENSA 1477
ND-AV-RS------------V--WE--K------------------------------------------K-G-D-V------------K------E--- 1477
GG-QA-KT------------M--MQ--R------------------------------------------E-M-G-K------------E------V--- 1458
                   IIIP                                IIIS6
MNFDHVGNAYLCLFQVATFKGWIQIMNDAIDSREVDKQPIRETNIYMYLYFVFFIIFGSFFTLNLFIGVIIDNFNEQKKKAGGSLEMFMTEDQKKYYNAM 1577
-------------------------------------------------------------------------------------------------N-- 1577
-------------------------------------------------------------------------------------------------S-- 1558
    •                                IVS1                              IVS2                       IVS3
KKMGSKKPLKAIPRPRWRPQAIVFEIVTDKKFDIIIMLFIGLNMFTMTLDRYDASEAYNNVLDKLNGIFVVIFSGECLLKIFALRYHYFKEPWNLFDVVV 1677
-------------------------------------------------------EA--N---K--G-------G--------------K---------- 1677
-------------------------------------------------------DT--A---Y--A-------S--------------I---------- 1658
```

FIG. 3C

```
                                      IVS4                                   IVS5
VILSILGLVLSDIIEKYFVSPTLLRVVRVAKVGRVLRLVKGAKGIRTLLFALAMSLPALFNICLLLFLVMFIFAIFGMSFFMHVKEKSGINAVYNFKTFG 1777
-------------------------------------------------------------------------------------------A-------- 1777
-------------------------------------------------------------------------------------------D-------- 1758

           IVP                                              IVS6    #
QSMILLFQMSTSAGWDGVLDAIINEEDCDPPDNDKGYPGNCGSATVGITFLLSYLVISFLIVINMYIAVILENYSQATEDVQEGLTDDDYDMYYEIWQQF 1877
--------------------------D------------------------------------------------------------------------- 1877
--------------------------A------------------------------------------------------------------------- 1858

DPEGTQYIRYDQLSEFLDVLEPPLQIHKPNKYKIISMDMPICRGDMMYCVDILDALTKDFFARKGNPIEETGEIGEIAARPDTEGYDPVSSTLWRQREEY 1977
--------------------------------------M------M----------------------------------------D------------- 1977
--------------------------------------I------L----------------------------------------E------------- 1958

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--K---N---RY-.........NGPPQE--E-EAAG-EDGAEGGEGEGGSG--GDDDG-S-T....-AGAT..SPTDPD-GE-DG-SAGNGG-PLSP-CV 2062
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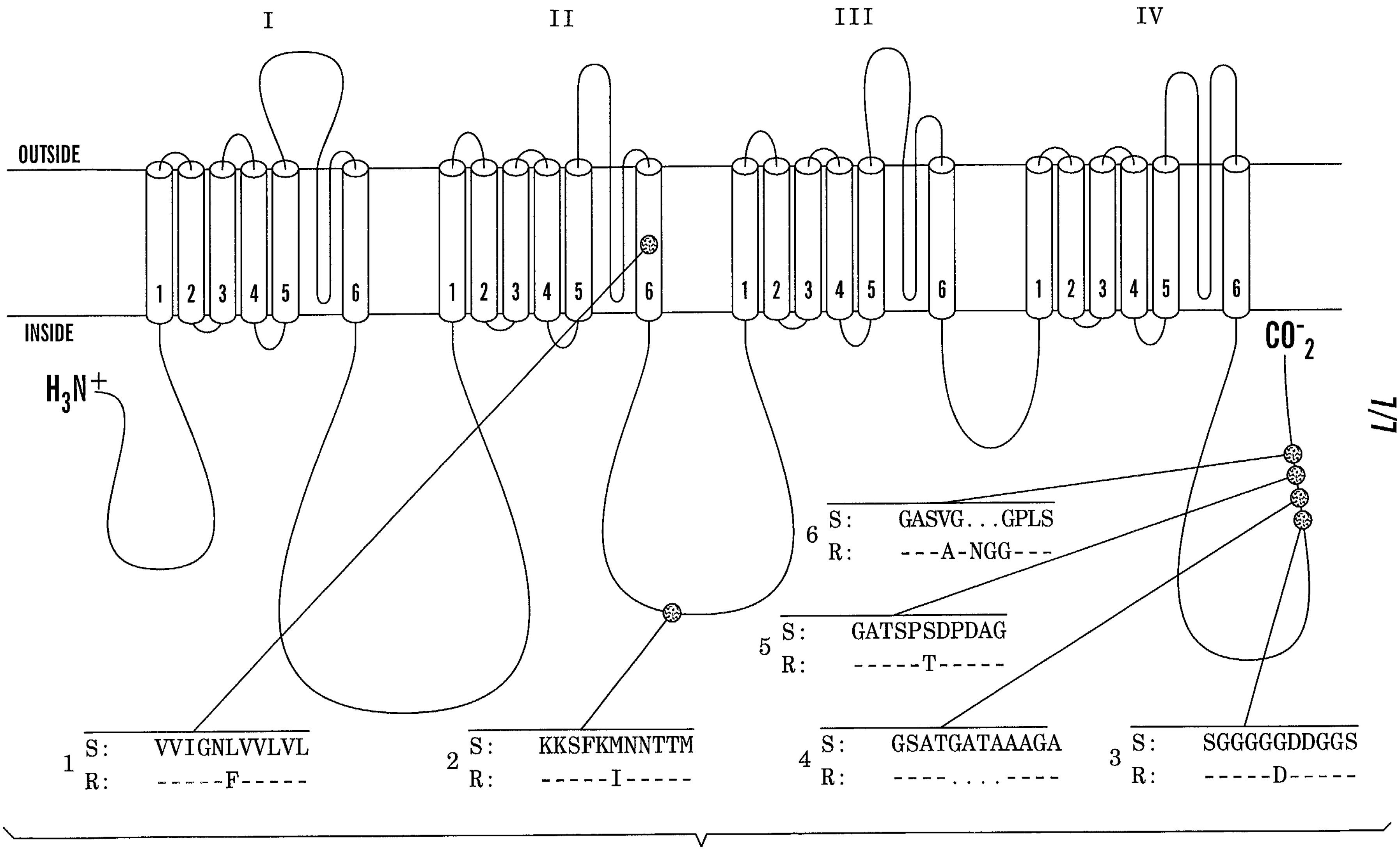
FIG. 3D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III
IV
OUTSIDE
INSIDE
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2 S: KKSFKMNNTTM
R: -----I-----
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R: ---A-NGG---
5 S: GATSPSDPDAG
R: -----T-----
4 S: GSATGATAAAGA
R: ----....----
3 S: SGGGGGDDGGS
R: -----D-----

FIG. 4

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
19603/601 (CRF D-1657)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES**

---

the specification of which (check only one item below):

[X] is attached hereto.

[ ] was filed as United States application
Serial No. ____
on ____
and was amended
on ____ (if applicable).

[ ] was filed as PCT international application
Number ____
on ____
and was amended under PCT Article 19
on ____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (IF PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

COMBINEL ECLARATION FOR PATENT APPLICATION AND 'OWER OF ATTORNEY (Continued) (Includes Reference t PCT International Applications)	ATTORNEY'S DOCKET NUMBER 19603/601 (CRF D-1657)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT International filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS			STATUS (Check One)		
U.S. APPLICATION NUMBER		U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/608,618		March 1, 1996		X	
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)
Susan J. Braman, Reg. No. 34,103, Michael L. Goldman, Reg. No. 30,727, Thomas Fitzgerald, Reg. No. 36,136, Gunnar Leinberg, Reg. No. 35,584, Peter Rogalskyj, Reg. No. 38,601, Karla Weyand, Reg. No. 40,223

Send Correspondence to: **Susan J. Braman, Esq.** **Nixon, Hargrave, Devans & Doyle LLP** **Clinton Square, P.O. Box 1051** **Rochester, New York 14603**	Direct Telephone Calls to: (name and telephone number) **Susan J. Braman** **(716) 263-1636**

201	FULL NAME OF INVENTOR	FAMILY NAME **SODERLUND**	FIRST GIVEN NAME **DAVID**	SECOND GIVEN NAME **M.**
	RESIDENCE & CITIZENSHIP	CITY **GENEVA**	STATE/FOREIGN COUNTRY **NEW YORK**	COUNTRY OF CITIZENSHIP **USA**
	POST OFFICE ADDRESS	P.O. ADDRESS **664 CASTLE STREET**	CITY **GENEVA**	STATE &ZIP CODE/COUNTRY **NEW YORK 14456/USA**
202	FULL NAME OF INVENTOR	FAMILY NAME **KNIPPLE**	FIRST GIVEN NAME **DOUGLAS**	SECOND GIVEN NAME **C.**
	RESIDENCE & CITIZENSHIP	CITY **GENEVA**	STATE/FOREIGN COUNTRY **NEW YORK**	COUNTRY OF CITIZENSHIP **USA**
	POST OFFICE ADDRESS	P.O. ADDRESS **109 MAXWELL AVENUE**	CITY **GENEVA**	STATE &ZIP CODE/COUNTRY **NEW YORK 14456/USA**
203	FULL NAME OF INVENTOR	FAMILY NAME **INGLES**	FIRST GIVEN NAME **PATRICIA**	SECOND GIVEN NAME **J.**
	RESIDENCE & CITIZENSHIP	CITY **GENEVA**	STATE/FOREIGN COUNTRY **NEW YORK**	COUNTRY OF CITIZENSHIP **GREAT BRITAIN**
	POST OFFICE ADDRESS	P.O. ADDRESS **85 HUMBERT STREET**	CITY **GENEVA**	STATE &ZIP CODE/COUNTRY **NEW YORK 14456/USA**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE	DATE	DATE

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER 19603/601 (CRF D-1657A)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES**

the specification of which (check only one item below):

[ ] is attached hereto.

[X] was filed as United States application
Serial No. 08/772,512
on December 24, 1996

[ ] was filed as PCT international application
Number ______
on ______
and was amended under PCT Article 19
on ______ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specifications, including the claims, as amended by any amendment referred to above.

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PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (IF PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			[ ] YES [ ] NO
			[ ] YES [ ] NO
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			[ ] YES [ ] NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued) (Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
19603/601 (CRF D-1657)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT International filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS			STATUS (Check One)		
U.S. APPLICATION NUMBER		U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/608,618		March 1, 1996		X	
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

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Send Correspondence to: **Susan J. Braman, Esq.**
Nixon, Hargrave, Devans & Doyle LLP
Clinton Square, P.O. Box 1051
Rochester, New York 14603

Direct Telephone Calls to: (name and telephone number)
Susan J. Braman
(716) 263-1636

201	FULL NAME OF INVENTOR	FAMILY NAME **SODERLUND**	FIRST GIVEN NAME **DAVID**	SECOND GIVEN NAME **M.**
	RESIDENCE & CITIZENSHIP	CITY **GENEVA**	STATE/FOREIGN COUNTRY **NEW YORK**	COUNTRY OF CITIZENSHIP **USA**
	POST OFFICE ADDRESS	P.O. ADDRESS **664 CASTLE STREET**	CITY **GENEVA**	STATE &ZIP CODE/COUNTRY **NEW YORK 14456/USA**
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203	FULL NAME OF INVENTOR	FAMILY NAME **INGLES**	FIRST GIVEN NAME **PATRICIA**	SECOND GIVEN NAME **J.**
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SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
Soderlund	Knipple	Ingles
DATE March 12, 1997	DATE Mar 12 1997	DATE March 12 1997.

ROC10:102192

SEQUENCE LISTING

<110> Soderlund, David M.
Knipple, Douglas C.
Ingles, Patricia J.

<120> INSECT SODIUM CHANNELS FROM INSECTICIDE-SUSCEPTIBLE AND INSECTICIDE-RESISTANT HOUSE FLIES

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Glu His Glu Lys Gln Lys Glu Leu Glu Arg Lys Arg Ala Ala Glu Gly
        35   40   45

Glu Gln Ile Arg Tyr Asp Asp Glu Asp Glu Asp Glu Gly Pro Gln Pro
    50   55   60

Asp Pro Thr Leu Glu Gln Gly Val Pro Ile Pro Val Arg Met Gln Gly
65   70   75   80

Ser Phe Pro Pro Glu Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro
                85   90   95

Phe Tyr Ser Asn Val Leu Thr Phe Val Val Ile Ser Lys Gly Lys Asp
            100   105   110

Ile Phe Arg Phe Ser Ala Ser Lys Ala Met Trp Leu Leu Asp Pro Phe
        115   120   125

Asn Pro Ile Arg Arg Val Ala Ile Tyr Ile Leu Val His Pro Leu Phe
    130   135   140

Ser Leu Phe Ile Ile Thr Thr Ile Leu Thr Asn Cys Ile Leu Met Ile
145   150   155   160

Met Pro Thr Thr Pro Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly
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Ile Tyr Thr Phe Glu Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile
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Leu Cys Pro Phe Thr Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe
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Val Val Ile Ala Leu Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn
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Leu Ala Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val
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Ala Ile Val Pro Gly Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser
245 250 255

Val Lys Asn Leu Arg Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser
260 265 270

Val Phe Ala Leu Met Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Gln
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Lys Cys Ile Lys Arg Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr
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Asp Glu Asn Trp Phe Leu His Asn Ser Asn Ser Ser Asn Trp Phe Thr
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Glu Asn Asp Gly Glu Ser Tyr Pro Val Cys Gly Asn Val Ser Gly Ala
325 330 335

Gly Gln Cys Gly Glu Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn
340 345 350

Pro Asn Tyr Asp Tyr Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu
355 360 365

Ser Ala Phe Arg Leu Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln
370 375 380

His Val Leu Gln Ala Ala Gly Pro Trp His Met Leu Phe Phe Ile Val
385 390 395 400

Ile Ile Phe Leu Gly Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile
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Val Ala Met Ser Tyr Asp Glu Leu Gln Lys Lys Ala Glu Glu Glu Glu
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Ala Ala Glu Glu Glu Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala
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Lys Ala Ala Lys Leu Glu Glu Arg Ala Asn Val Ala Ala Gln Ala Ala
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Gln Asp Ala Ala Asp Ala Ala Ala Ala Ala Leu His Pro Glu Met Ala
465 470 475 480

Lys Ser Pro Thr Tyr Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly
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Glu Lys Gly Asn Asp Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser
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Val Glu Val Glu Ser Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala
515 520 525

Pro Thr Thr Ala Pro Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser
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Leu Ser Leu Pro Gly Ser Pro Phe Asn Leu Arg Arg Gly Ser Arg Ser
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Ser His Lys Tyr Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro
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Gly Ser Asp Arg Lys Pro Leu Val Leu Gln Thr Tyr Gln Asp Ala Gln
580 585 590

Gln His Leu Pro Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser
595 600 605

Glu Glu Asn Gly Ala Ile Ile Val Pro Ala Tyr Tyr Cys Asn Leu Gly
610 615 620

Ser Arg His Ser Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr
625 630 635 640

Ser His Gly Asp Leu Leu Gly Gly Met Ala Ala Met Gly Ala Ser Thr
645 650 655

Met Thr Lys Glu Ser Lys Leu Arg Ser Arg Asn Thr Arg Asn Gln Ser
660 665 670

Ile Gly Ala Ala Thr Asn Gly Gly Ser Ser Thr Ala Gly Gly Gly Tyr
675 680 685

Pro Asp Ala Asn His Lys Glu Gln Arg Asp Tyr Glu Met Gly Gln Asp
    690   695   700

Tyr Thr Asp Glu Ala Gly Lys Ile Lys His His Asp Asn Pro Phe Ile
705   710   715   720

Glu Pro Val Gln Thr Gln Thr Val Val Asp Met Lys Asp Val Met Val
                725   730   735

Leu Asn Asp Ile Ile Glu Gln Ala Ala Gly Arg His Ser Arg Ala Ser
            740   745   750

Glu Arg Gly Glu Asp Asp Asp Glu Asp Gly Pro Thr Phe Lys Asp Ile
        755   760   765

Ala Leu Glu Tyr Ile Leu Lys Gly Ile Glu Ile Phe Cys Val Trp Asp
    770   775   780

Cys Cys Trp Val Trp Leu Lys Phe Gln Glu Trp Val Ser Phe Ile Val
785   790   795   800

Phe Asp Pro Phe Val Glu Leu Phe Ile Thr Leu Cys Ile Val Val Asn
                805   810   815

Thr Met Phe Met Ala Met Asp His His Asp Met Asn Pro Glu Leu Glu
            820   825   830

Lys Val Leu Lys Ser Gly Asn Tyr Phe Phe Thr Ala Thr Phe Ala Ile
        835   840   845

Glu Ala Ser Met Lys Leu Met Ala Met Ser Pro Lys Tyr Tyr Phe Gln
    850   855   860

Glu Gly Trp Asn Ile Phe Asp Phe Ile Ile Val Ala Leu Ser Leu Leu
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Glu Leu Gly Leu Glu Gly Val Gln Gly Leu Ser Val Leu Arg Ser Phe
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Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn
            900   905   910

Leu Leu Ile Ser Ile Met Gly Arg Thr Met Gly Ala Leu Gly Asn Leu
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Thr Phe Val Leu Cys Ile Ile Ile Phe Ile Phe Ala Val Met Gly Met
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Gln Leu Phe Gly Lys Asn Tyr Ile Asp His Lys Asp Arg Phe Lys Asp
945 950 955 960

His Glu Leu Pro Arg Trp Asn Phe Thr Asp Phe Met His Ser Phe Met
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Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Ser Met Trp Asp
980 985 990

Cys Met Tyr Val Gly Asp Val Ser Cys Ile Pro Phe Phe Leu Ala Thr
995 1000 1005

Val Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu
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Leu Ser Asn Phe Gly Ser Ser Ser Leu Ser Ala Pro Thr Ala Asp Asn
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Asp Thr Asn Lys Ile Ala Glu Ala Phe Asn Arg Ile Ala Arg Phe Lys
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Asn Trp Val Lys Arg Asn Ile Ala Asp Cys Phe Lys Leu Ile Arg Asn
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Lys Leu Thr Asn Gln Ile Ser Asp Gln Pro Ser Glu His Gly Asp Asn
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Glu Leu Glu Leu Gly His Asp Glu Ile Met Gly Asp Gly Leu Ile Lys
1090 1095 1100

Lys Gly Met Lys Gly Glu Thr Gln Leu Glu Val Ala Ile Gly Asp Gly
1105 1110 1115 1120

Met Glu Phe Thr Ile His Gly Asp Met Lys Asn Asn Lys Pro Lys Lys
1125 1130 1135

Ser Lys Phe Met Asn Asn Thr Thr Met Ile Gly Asn Ser Ile Asn His
1140 1145 1150

Gln Asp Asn Arg Leu Glu His Glu Leu Asn His Arg Gly Leu Ser Ile
1155 1160 1165

Gln Asp Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn
1170 1175 1180

Arg Pro Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Ile Glu
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Gly Glu Glu Lys Arg Asp Val Ser Lys Glu Asp Leu Gly Leu Asp Glu
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Glu Leu Asp Glu Glu Ala Glu Gly Asp Glu Gly Gln Leu Asp Gly Asp
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Ile Ile Ile His Ala Gln Asn Asp Asp Glu Ile Ile Asp Asp Tyr Pro
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Gly Asp Glu Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu
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Lys Thr Phe Gln Leu Ile Glu Asn Lys Tyr Phe Glu Thr Ala Val Ile
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Ile Phe Thr Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala
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Leu Gly Phe Lys Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe
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Val Ile Val Met Leu Ser Leu Ile Asn Leu Val Ala Val Trp Ser Gly
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Leu Asn Asp Ile Ala Val Phe Arg Ser Met Arg Thr Leu Arg Ala Leu
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Asn Ala Leu Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val
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Cys Leu Ile Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe
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Ala Gly Lys Tyr Phe Lys Cys Lys Asp Gly Asn Asp Thr Val Leu Ser
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His Glu Ile Ile Pro Asn Arg Asn Ala Cys Lys Ser Glu Asn Tyr Thr
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Trp Glu Asn Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu
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Cys Leu Phe Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn
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Asp Ala Ile Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr
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Asn Ile Tyr Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser
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Asp Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Met Gly Ser Lys Lys
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Pro Leu Lys Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val
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Phe Glu Ile Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe
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Ile Gly Leu Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser
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Glu Ala Tyr Asn Asn Val Leu Asp Lys Leu Asn Gly Ile Phe Val Val
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Ile Phe Ser Gly Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His
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Tyr Phe Lys Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu
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Ser Ile Leu Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val
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Ser Pro Thr Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val
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Leu Arg Leu Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala
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Leu Ala Met Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe
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Leu Val Met Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His
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Val Lys Glu Lys Ser Gly Ile Asn Ala Val Tyr Asn Phe Lys Thr Phe
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Asp Gly Val Leu Asp Ala Ile Ile Asn Glu Glu Asp Cys Asp Pro Pro
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Asp Asn Asp Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly
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Ile Thr Phe Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile
1825 1830 1835 1840

Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu
1845 1850 1855

Asp Val Gln Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu
1860 1865 1870

Ile Trp Gln Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp
1875 1880 1885

Gln Leu Ser Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His
1890 1895 1900

Lys Pro Asn Lys Tyr Lys Ile Ile Ser Met Asp Met Pro Ile Cys Arg
1905 1910 1915 1920

Gly Asp Met Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp
1925 1930 1935

Phe Phe Ala Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly
1940 1945 1950

Glu Ile Ala Ala Arg Pro Asp Thr Glu Gly Tyr Asp Pro Val Ser Ser
1955 1960 1965

Thr Leu Trp Arg Gln Arg Glu Glu Tyr Cys Ala Lys Leu Ile Gln Asn
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1985   1990   1995   2000

Glu Ala Ala Gly Gly Glu Asp Gly Ala Glu Gly Gly Glu Gly Glu Gly
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Thr Ala Ala Ala Gly Ala Thr Ser Pro Ser Asp Pro Asp Ala Gly Glu
        2035   2040   2045

Ala Asp Gly Ala Ser Val Gly Gly Pro Leu Ser Pro Gly Cys Val Ser
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Gly Gly Ser Asn Gly Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly
2065   2070   2075   2080

Phe Val Thr Lys Asn Gly His Lys Val Val Ile His Ser Arg Ser Pro
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Ser Phe Pro Pro Glu Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro
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Ser Leu Phe Ile Ile Thr Thr Ile Leu Thr Asn Cys Ile Leu Met Ile
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Met Pro Thr Thr Pro Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly
165 170 175

Ile Tyr Thr Phe Glu Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile
180 185 190

Leu Cys Pro Phe Thr Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe
195 200 205

Val Val Ile Ala Leu Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn
210 215 220

Leu Ala Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val
225 230 235 240

Ala Ile Val Pro Gly Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser
245 250 255

Val Lys Asn Leu Arg Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser
260 265 270

Val Phe Ala Leu Met Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Gln
275 280 285

Lys Cys Ile Lys Arg Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr
290 295 300

Asp Glu Asn Trp Phe Leu His Asn Ser Asn Ser Ser Asn Trp Phe Thr
305 310 315 320

Glu Asn Asp Gly Glu Ser Tyr Pro Val Cys Gly Asn Val Ser Gly Ala

325 330 335

Gly Gln Cys Gly Glu Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn
340 345 350

Pro Asn Tyr Asp Tyr Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu
355 360 365

Ser Ala Phe Arg Leu Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln
370 375 380

His Val Leu Gln Ala Ala Gly Pro Trp His Met Leu Phe Phe Ile Val
385 390 395 400

Ile Ile Phe Leu Gly Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile
405 410 415

Val Ala Met Ser Tyr Asp Glu Leu Gln Lys Lys Ala Glu Glu Glu Glu
420 425 430

Ala Ala Glu Glu Glu Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala
435 440 445

Lys Ala Ala Lys Leu Glu Glu Arg Ala Asn Val Ala Ala Gln Ala Ala
450 455 460

Gln Asp Ala Ala Asp Ala Ala Ala Ala Ala Leu His Pro Glu Met Ala
465 470 475 480

Lys Ser Pro Thr Tyr Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly
485 490 495

Glu Lys Gly Asn Asp Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser
500 505 510

Val Glu Val Glu Ser Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala
515 520 525

Pro Thr Thr Ala Pro Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser
530 535 540

Leu Ser Leu Pro Gly Ser Pro Phe Asn Leu Arg Arg Gly Ser Arg Ser
545 550 555 560

Ser His Lys Tyr Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro
565 570 575

Gly Ser Asp Arg Lys Pro Leu Val Leu Gln Thr Tyr Gln Asp Ala Gln

580 585 590

Gln His Leu Pro Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser
595 600 605

Glu Glu Asn Gly Ala Ile Ile Val Pro Ala Tyr Tyr Cys Asn Leu Gly
610 615 620

Ser Arg His Ser Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr
625 630 635 640

Ser His Gly Asp Leu Leu Gly Gly Met Ala Ala Met Gly Ala Ser Thr
645 650 655

Met Thr Lys Glu Ser Lys Leu Arg Ser Arg Asn Thr Arg Asn Gln Ser
660 665 670

Ile Gly Ala Ala Thr Asn Gly Gly Ser Ser Thr Ala Gly Gly Gly Tyr
675 680 685

Pro Asp Ala Asn His Lys Glu Gln Arg Asp Tyr Glu Met Gly Gln Asp
690 695 700

Tyr Thr Asp Glu Ala Gly Lys Ile Lys His His Asp Asn Pro Phe Ile
705 710 715 720

Glu Pro Val Gln Thr Gln Thr Val Val Asp Met Lys Asp Val Met Val
725 730 735

Leu Asn Asp Ile Ile Glu Gln Ala Ala Gly Arg His Ser Arg Ala Ser
740 745 750

Glu Arg Gly Glu Asp Asp Asp Glu Asp Gly Pro Thr Phe Lys Asp Ile
755 760 765

Ala Leu Glu Tyr Ile Leu Lys Gly Ile Glu Ile Phe Cys Val Trp Asp
770 775 780

Cys Cys Trp Val Trp Leu Lys Phe Gln Glu Trp Val Ser Phe Ile Val
785 790 795 800

Phe Asp Pro Phe Val Glu Leu Phe Ile Thr Leu Cys Ile Val Val Asn
805 810 815

Thr Met Phe Met Ala Met Asp His His Asp Met Asn Pro Glu Leu Glu
820 825 830

Lys Val Leu Lys Ser Gly Asn Tyr Phe Phe Thr Ala Thr Phe Ala Ile

835 840 845

Glu Ala Ser Met Lys Leu Met Ala Met Ser Pro Lys Tyr Tyr Phe Gln
850 855 860

Glu Gly Trp Asn Ile Phe Asp Phe Ile Ile Val Ala Leu Ser Leu Leu
865 870 875 880

Glu Leu Gly Leu Glu Gly Val Gln Gly Leu Ser Val Leu Arg Ser Phe
885 890 895

Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn
900 905 910

Leu Leu Ile Ser Ile Met Gly Arg Thr Met Gly Ala Leu Gly Asn Leu
915 920 925

Thr Phe Val Leu Cys Ile Ile Ile Phe Ile Phe Ala Val Met Gly Met
930 935 940

Gln Leu Phe Gly Lys Asn Tyr Ile Asp His Lys Asp Arg Phe Lys Asp
945 950 955 960

His Glu Leu Pro Arg Trp Asn Phe Thr Asp Phe Met His Ser Phe Met
965 970 975

Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Ser Met Trp Asp
980 985 990

Cys Met Tyr Val Gly Asp Val Ser Cys Ile Pro Phe Phe Leu Ala Thr
995 1000 1005

Val Val Ile Gly Asn Phe Val Val Leu Asn Leu Phe Leu Ala Leu Leu
1010 1015 1020

Leu Ser Asn Phe Gly Ser Ser Ser Leu Ser Ala Pro Thr Ala Asp Asn
1025 1030 1035 1040

Asp Thr Asn Lys Ile Ala Glu Ala Phe Asn Arg Ile Ala Arg Phe Lys
1045 1050 1055

Asn Trp Val Lys Arg Asn Ile Ala Asp Cys Phe Lys Leu Ile Arg Asn
1060 1065 1070

Lys Leu Thr Asn Gln Ile Ser Asp Gln Pro Ser Glu His Gly Asp Asn
1075 1080 1085

Glu Leu Glu Leu Gly His Asp Glu Ile Met Gly Asp Gly Leu Ile Lys

1090 1095 1100

Lys Gly Met Lys Gly Glu Thr Gln Leu Glu Val Ala Ile Gly Asp Gly
1105 1110 1115 1120

Met Glu Phe Thr Ile His Gly Asp Met Lys Asn Asn Lys Pro Lys Lys
1125 1130 1135

Ser Lys Phe Ile Asn Asn Thr Thr Met Ile Gly Asn Ser Ile Asn His
1140 1145 1150

Gln Asp Asn Arg Leu Glu His Glu Leu Asn His Arg Gly Leu Ser Ile
1155 1160 1165

Gln Asp Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn
1170 1175 1180

Arg Pro Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Ile Glu
1185 1190 1195 1200

Gly Glu Glu Lys Arg Asp Val Ser Lys Glu Asp Leu Gly Leu Asp Glu
1205 1210 1215

Glu Leu Asp Glu Glu Ala Glu Gly Asp Glu Gly Gln Leu Asp Gly Asp
1220 1225 1230

Ile Ile Ile His Ala Gln Asn Asp Asp Glu Ile Ile Asp Asp Tyr Pro
1235 1240 1245

Ala Asp Cys Phe Pro Asp Ser Tyr Tyr Lys Lys Phe Pro Ile Leu Ala
1250 1255 1260

Gly Asp Glu Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu
1265 1270 1275 1280

Lys Thr Phe Gln Leu Ile Glu Asn Lys Tyr Phe Glu Thr Ala Val Ile
1285 1290 1295

Thr Met Ile Leu Met Ser Ser Leu Ala Leu Ala Leu Glu Asp Val His
1300 1305 1310

Leu Pro Asp Arg Pro Val Met Gln Asp Ile Leu Tyr Tyr Met Asp Arg
1315 1320 1325

Ile Phe Thr Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala
1330 1335 1340

Leu Gly Phe Lys Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe

1345 1350 1355 1360

Val Ile Val Met Leu Ser Leu Ile Asn Leu Val Ala Val Trp Ser Gly
1365 1370 1375

Leu Asn Asp Ile Ala Val Phe Arg Ser Met Arg Thr Leu Arg Ala Leu
1380 1385 1390

Arg Pro Leu Arg Ala Val Ser Arg Trp Glu Gly Met Lys Val Val Val
1395 1400 1405

Asn Ala Leu Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val
1410 1415 1420

Cys Leu Ile Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe
1425 1430 1435 1440

Ala Gly Lys Tyr Phe Lys Cys Lys Asp Gly Asn Asp Thr Val Leu Ser
1445 1450 1455

His Glu Ile Ile Pro Asn Arg Asn Ala Cys Lys Ser Glu Asn Tyr Thr
1460 1465 1470

Trp Glu Asn Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu
1475 1480 1485

Cys Leu Phe Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn
1490 1495 1500

Asp Ala Ile Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr
1505 1510 1515 1520

Asn Ile Tyr Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser
1525 1530 1535

Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn
1540 1545 1550

Glu Gln Lys Lys Lys Ala Gly Gly Ser Leu Glu Met Phe Met Thr Glu
1555 1560 1565

Asp Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Met Gly Ser Lys Lys
1570 1575 1580

Pro Leu Lys Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val
1585 1590 1595 1600

Phe Glu Ile Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe

1605 1610 1615

Ile Gly Leu Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser
1620 1625 1630

Glu Ala Tyr Asn Asn Val Leu Asp Lys Leu Asn Gly Ile Phe Val Val
1635 1640 1645

Ile Phe Ser Gly Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His
1650 1655 1660

Tyr Phe Lys Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu
1665 1670 1675 1680

Ser Ile Leu Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val
1685 1690 1695

Ser Pro Thr Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val
1700 1705 1710

Leu Arg Leu Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala
1715 1720 1725

Leu Ala Met Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe
1730 1735 1740

Leu Val Met Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His
1745 1750 1755 1760

Val Lys Glu Lys Ser Gly Ile Asn Ala Val Tyr Asn Phe Lys Thr Phe
1765 1770 1775

Gly Gln Ser Met Ile Leu Leu Phe Gln Met Ser Thr Ser Ala Gly Trp
1780 1785 1790

Asp Gly Val Leu Asp Ala Ile Ile Asn Glu Glu Asp Cys Asp Pro Pro
1795 1800 1805

Asp Asn Asp Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly
1810 1815 1820

Ile Thr Phe Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile
1825 1830 1835 1840

Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu
1845 1850 1855

Asp Val Gln Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu

1860 1865 1870

Ile Trp Gln Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp
1875 1880 1885

Gln Leu Ser Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His
1890 1895 1900

Lys Pro Asn Lys Tyr Lys Ile Ile Ser Met Asp Met Pro Ile Cys Arg
1905 1910 1915 1920

Gly Asp Met Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp
1925 1930 1935

Phe Phe Ala Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly
1940 1945 1950

Glu Ile Ala Ala Arg Pro Asp Thr Glu Gly Tyr Asp Pro Val Ser Ser
1955 1960 1965

Thr Leu Trp Arg Gln Arg Glu Glu Tyr Cys Ala Lys Leu Ile Gln Asn
1970 1975 1980

Ala Trp Arg Arg Tyr Lys Asn Gly Pro Pro Gln Glu Gly Asp Glu Gly
1985 1990 1995 2000

Glu Ala Ala Gly Gly Glu Asp Gly Ala Glu Gly Gly Glu Gly Glu Gly
2005 2010 2015

Gly Ser Gly Gly Gly Gly Asp Asp Asp Gly Gly Ser Ala Thr Ala Ala
2020 2025 2030

Gly Ala Thr Ser Pro Thr Asp Pro Asp Ala Gly Glu Ala Asp Gly Ala
2035 2040 2045

Ser Ala Gly Asn Gly Gly Gly Pro Leu Ser Pro Gly Cys Val Ser Gly
2050 2055 2060

Gly Ser Asn Gly Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly Phe
2065 2070 2075 2080

Val Thr Lys Asn Gly His Lys Val Val Ile His Ser Arg Ser Pro Ser
2085 2090 2095

Ile Thr Ser Arg Thr Ala Asp Val
2100

<210> 5
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<400> 5
cggttgggct ttcctgtc 18

<210> 6
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<220>
<221> unsure
<222> (21)
<223> N at position 21 is either A, C, G, or T

<400> 6
gggaattcra adatrttcca nccytc 26

<210> 7
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<220>
<221> unsure
<222> (18)
<223> N at position 18 is either A, C, G, or T

<400> 7
cccgargaya thgaycynta yta 23

<210> 8
<211> 18

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vssc1 cDNAs.

<400> 8
cgtatcgcct cctcctcg 18

<210> 9
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vssc1 cDNAs.

<220>
<221> unsure
<222> (17)
<223> N at any position in this sequence is A, C, G, or
T

<400> 9
gggtctagat httygcnath ttyggnatg 29

<210> 10
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vssc1 cDNAs.

<220>
<221> unsure
<222> (10)
<223> N at position 10 is either A, C, G, or T

<400> 10
ggggaattcn ggrtcraayt gytgcca 27

<210> 11
<211> 27
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<220>
<221> unsure
<222> (13)
<223> N at position 13 is either A, C, G, or T

<400> 11
gggtctagar gancaraara artayta 27

<210> 12
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<400> 12
tcatactttg gcccaatgtc 20

<210> 13
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<400> 13
cccgaattag agaaggtgct g 21

<210> 14
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vsscl cDNAs.

<400> 14

actattgctt gtggtcgcca c 21

<210> 15
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vssc1 cDNAs.

<220>
<221> unsure
<222> (5)
<223> N at any position in this sequence is A, C, G, or
T

<400> 15
catcnttrgc ngcntagacn atgac 25

<210> 16
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primers for PCR amplification of Vssc1 cDNAs.

<400> 16
gattgaatgg atcgagcagc c 21

<210> 17
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
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primers for PCR amplification of Vssc1 cDNAs.

<400> 17
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<210> 18
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<212> DNA
<213> Artificial Sequence

<220>
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primers for PCR amplification of Vssc1 cDNAs.

<220>
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<223> N at any position in this sequence is A, C, G, or
T

<400> 18
ggagbggbgg nckbggnckn gctca 25

<210> 19
<211> 2100
<212> PRT
<213> Drosophila melanogaster

<400> 19
Met Thr Glu Asp Ser Asp Ser Ile Ser Glu Glu Glu Arg Ser Leu Phe
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Arg Pro Phe Thr Arg Glu Ser Leu Val Gln Ile Glu Gln Arg Ile Ala
20 25 30

Ala Glu His Glu Lys Gln Lys Glu Leu Glu Arg Lys Arg Ala Glu Gly
35 40 45

Glu Val Pro Arg Tyr Gly Arg Lys Lys Lys Gln Lys Glu Ile Arg Tyr
50 55 60

Asp Asp Glu Asp Glu Asp Glu Gly Pro Gln Pro Asp Pro Thr Leu Glu
65 70 75 80

Gln Gly Val Pro Ile Pro Val Arg Leu Gln Gly Ser Phe Pro Pro Glu
85 90 95

Leu Ala Ser Thr Pro Leu Glu Asp Ile Asp Pro Tyr Tyr Ser Asn Val
100 105 110

Leu Thr Phe Val Val Val Ser Lys Gly Lys Asp Ile Phe Arg Phe Ser
115 120 125

Ala Ser Lys Ala Met Trp Met Leu Asp Pro Phe Asn Pro Ile Arg Arg
130 135 140

Val Ala Ile Tyr Ile Leu Val His Pro Leu Phe Ser Leu Phe Ile Ile

145 150 155 160

Thr Thr Ile Leu Val Asn Cys Ile Leu Met Ile Met Pro Thr Thr Pro
165 170 175

Thr Val Glu Ser Thr Glu Val Ile Phe Thr Gly Ile Tyr Thr Phe Glu
180 185 190

Ser Ala Val Lys Val Met Ala Arg Gly Phe Ile Leu Cys Pro Phe Thr
195 200 205

Tyr Leu Arg Asp Ala Trp Asn Trp Leu Asp Phe Val Val Ile Ala Leu
210 215 220

Ala Tyr Val Thr Met Gly Ile Asp Leu Gly Asn Leu Ala Ala Leu Arg
225 230 235 240

Thr Phe Arg Val Leu Arg Ala Leu Lys Thr Val Ala Ile Val Pro Gly
245 250 255

Leu Lys Thr Ile Val Gly Ala Val Ile Glu Ser Val Lys Asn Leu Arg
260 265 270

Asp Val Ile Ile Leu Thr Met Phe Ser Leu Ser Val Phe Ala Leu Met
275 280 285

Gly Leu Gln Ile Tyr Met Gly Val Leu Thr Glu Lys Cys Ile Lys Lys
290 295 300

Phe Pro Leu Asp Gly Ser Trp Gly Asn Leu Thr Asp Glu Asn Trp Asp
305 310 315 320

Tyr His Asn Arg Asn Ser Ser Asn Trp Tyr Ser Glu Asp Glu Gly Ile
325 330 335

Ser Phe Pro Leu Cys Gly Asn Ile Ser Gly Ala Gly Gln Cys Asp Asp
340 345 350

Asp Tyr Val Cys Leu Gln Gly Phe Gly Pro Asn Pro Asn Tyr Gly Tyr
355 360 365

Thr Ser Phe Asp Ser Phe Gly Trp Ala Phe Leu Ser Ala Phe Arg Leu
370 375 380

Met Thr Gln Asp Phe Trp Glu Asp Leu Tyr Gln Leu Val Leu Arg Ala
385 390 395 400

Ala Gly Pro Trp His Met Leu Phe Phe Ile Val Ile Ile Phe Leu Gly

405 410 415

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Ile Val Ala Met Ser Tyr
420 425 430

Asp Glu Leu Gln Arg Lys Ala Glu Glu Glu Glu Ala Ala Glu Glu Glu
435 440 445

Ala Ile Arg Glu Ala Glu Glu Ala Ala Ala Ala Lys Ala Ala Lys Leu
450 455 460

Glu Glu Arg Ala Asn Ala Gln Ala Gln Ala Ala Ala Asp Ala Ala Ala
465 470 475 480

Ala Glu Glu Ala Ala Leu His Pro Glu Met Ala Lys Ser Pro Thr Tyr
485 490 495

Ser Cys Ile Ser Tyr Glu Leu Phe Val Gly Gly Glu Lys Gly Asn Asp
500 505 510

Asp Asn Asn Lys Glu Lys Met Ser Ile Arg Ser Val Glu Val Glu Ser
515 520 525

Glu Ser Val Ser Val Ile Gln Arg Gln Pro Ala Pro Thr Thr Ala His
530 535 540

Gln Ala Thr Lys Val Arg Lys Val Ser Thr Thr Ser Leu Ser Leu Pro
545 550 555 560

Gly Ser Pro Phe Asn Ile Arg Arg Gly Ser Arg Ser Ser His Lys Tyr
565 570 575

Thr Ile Arg Asn Gly Arg Gly Arg Phe Gly Ile Pro Gly Ser Asp Arg
580 585 590

Lys Pro Leu Val Leu Ser Thr Tyr Gln Asp Ala Gln Gln His Leu Pro
595 600 605

Tyr Ala Asp Asp Ser Asn Ala Val Thr Pro Met Ser Glu Glu Asn Gly
610 615 620

Ala Ile Ile Val Pro Val Tyr Tyr Gly Asn Leu Gly Ser Arg His Ser
625 630 635 640

Ser Tyr Thr Ser His Gln Ser Arg Ile Ser Tyr Thr Ser His Gly Asp
645 650 655

Leu Leu Gly Gly Met Ala Val Met Gly Val Ser Thr Met Thr Lys Glu

660 665 670

Ser Lys Leu Arg Asn Arg Asn Thr Arg Asn Gln Ser Val Gly Ala Thr
675 680 685

Asn Gly Gly Thr Thr Cys Leu Asp Thr Asn His Lys Leu Asp His Arg
690 695 700

Asp Tyr Glu Ile Gly Leu Glu Cys Thr Asp Glu Ala Gly Lys Ile Lys
705 710 715 720

His His Asp Asn Pro Phe Ile Glu Pro Val Gln Thr Gln Thr Val Val
725 730 735

Asp Met Lys Asp Val Met Val Leu Asn Asp Ile Ile Glu Gln Ala Ala
740 745 750

Gly Arg His Ser Arg Ala Ser Asp Arg Gly Glu Asp Asp Asp Glu Asp
755 760 765

Gly Pro Thr Phe Lys Asp Lys Ala Leu Glu Val Ile Leu Lys Gly Ile
770 775 780

Asp Val Phe Cys Val Trp Asp Cys Cys Trp Val Trp Leu Lys Phe Gln
785 790 795 800

Glu Trp Val Ser Leu Ile Val Phe Asp Pro Phe Val Glu Leu Phe Ile
805 810 815

Thr Leu Cys Ile Val Val Asn Thr Met Phe Met Ala Met Asp His His
820 825 830

Asp Met Asn Lys Glu Met Glu Arg Val Leu Lys Ser Gly Asn Tyr Phe
835 840 845

Phe Thr Ala Thr Phe Ala Ile Glu Ala Thr Met Lys Leu Met Ala Met
850 855 860

Ser Pro Lys Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Phe Ile
865 870 875 880

Ile Val Ala Leu Ser Leu Leu Glu Leu Gly Leu Glu Gly Val Gln Gly
885 890 895

Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala
900 905 910

Lys Ser Trp Pro Thr Leu Asn Leu Leu Ile Ser Ile Met Gly Arg Thr

915 920 925

Met Gly Ala Leu Gly Asn Leu Thr Phe Val Leu Cys Ile Ile Ile Phe
930 935 940

Ile Phe Ala Val Met Gly Met Gln Leu Phe Gly Lys Asn Tyr His Asp
945 950 955 960

His Lys Asp Arg Phe Pro Asp Gly Asp Leu Pro Arg Trp Asn Phe Thr
965 970 975

Asp Phe Met His Ser Phe Met Ile Val Phe Arg Val Leu Cys Gly Glu
980 985 990

Trp Ile Glu Ser Met Trp Asp Cys Met Tyr Val Gly Asp Val Ser Cys
995 1000 1005

Ile Pro Phe Phe Leu Ala Thr Val Val Ile Gly Asn Leu Val Val Leu
1010 1015 1020

Asn Leu Phe Leu Ala Leu Leu Leu Ser Asn Phe Gly Ser Ser Ser Leu
1025 1030 1035 1040

Ser Ala Pro Thr Ala Asp Asn Asp Thr Asn Lys Ile Ala Glu Ala Phe
1045 1050 1055

Asn Arg Ile Gly Arg Phe Lys Ser Trp Val Lys Arg Asn Ile Ala Asp
1060 1065 1070

Cys Phe Lys Leu Ile Arg Asn Lys Leu Thr Asn Gln Ile Ser Asp Gln
1075 1080 1085

Pro Ser Glu His Gly Asp Asn Glu Leu Glu Leu Gly His Asp Glu Ile
1090 1095 1100

Leu Ala Asp Gly Leu Ile Lys Lys Gly Ile Lys Glu Gln Thr Gln Leu
1105 1110 1115 1120

Glu Val Ala Ile Gly Asp Gly Met Glu Phe Thr Ile His Gly Asp Met
1125 1130 1135

Lys Asn Asn Lys Pro Lys Lys Ser Lys Tyr Leu Asn Asn Ala Thr Asp
1140 1145 1150

Asp Asp Thr Ala Ser Ile Asn Ser Tyr Gly Ser His Lys Asn Arg Pro
1155 1160 1165

Phe Lys Asp Glu Ser His Lys Gly Ser Ala Glu Thr Met Glu Gly Glu

1170 1175 1180

Glu Lys Arg Asp Ala Ser Lys Glu Asp Leu Gly Leu Asp Glu Glu Leu
1185 1190 1195 1200

Asp Glu Glu Gly Glu Cys Glu Glu Gly Pro Leu Asp Gly Asp Ile Ile
1205 1210 1215

Ile His Ala His Asp Glu Asp Ile Leu Asp Glu Tyr Pro Ala Asp Cys
1220 1225 1230

Cys Pro Asp Ser Tyr Tyr Lys Lys Phe Pro Ile Leu Ala Gly Asp Asp
1235 1240 1245

Asp Ser Pro Phe Trp Gln Gly Trp Gly Asn Leu Arg Leu Lys Thr Phe
1250 1255 1260

Arg Leu Ile Glu Asp Lys Tyr Phe Glu Thr Ala Val Ile Thr Met Ile
1265 1270 1275 1280

Leu Met Ser Ser Leu Ala Leu Ala Leu Glu Asp Val His Leu Pro Gln
1285 1290 1295

Arg Pro Ile Leu Gln Asp Ile Leu Tyr Tyr Met Asp Arg Ile Phe Thr
1300 1305 1310

Val Ile Phe Phe Leu Glu Met Leu Ile Lys Trp Leu Ala Leu Gly Phe
1315 1320 1325

Lys Val Tyr Leu Thr Asn Ala Trp Cys Trp Leu Asp Phe Val Ile Val
1330 1335 1340

Met Val Ser Leu Ile Asn Phe Val Ala Ser Leu Val Gly Ala Gly Gly
1345 1350 1355 1360

Ile Gln Ala Phe Lys Thr Met Arg Thr Leu Arg Ala Leu Arg Pro Leu
1365 1370 1375

Arg Ala Met Ser Arg Met Gln Gly Met Arg Val Val Val Asn Ala Leu
1380 1385 1390

Val Gln Ala Ile Pro Ser Ile Phe Asn Val Leu Leu Val Cys Leu Ile
1395 1400 1405

Phe Trp Leu Ile Phe Ala Ile Met Gly Val Gln Leu Phe Ala Gly Lys
1410 1415 1420

Tyr Phe Lys Cys Glu Asp Met Asn Gly Thr Lys Leu Ser His Glu Ile

1425 1430 1435 1440

Ile Pro Asn Arg Asn Ala Cys Glu Ser Glu Asn Tyr Thr Trp Val Asn
1445 1450 1455

Ser Ala Met Asn Phe Asp His Val Gly Asn Ala Tyr Leu Cys Leu Phe
1460 1465 1470

Gln Val Ala Thr Phe Lys Gly Trp Ile Gln Ile Met Asn Asp Ala Ile
1475 1480 1485

Asp Ser Arg Glu Val Asp Lys Gln Pro Ile Arg Glu Thr Asn Ile Tyr
1490 1495 1500

Met Tyr Leu Tyr Phe Val Phe Phe Ile Ile Phe Gly Ser Phe Phe Thr
1505 1510 1515 1520

Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Glu Gln Lys
1525 1530 1535

Lys Lys Ala Gly Gly Ser Leu Glu Met Phe Met Thr Glu Asp Gln Lys
1540 1545 1550

Lys Tyr Tyr Ser Ala Met Lys Lys Met Gly Ser Lys Lys Pro Leu Lys
1555 1560 1565

Ala Ile Pro Arg Pro Arg Trp Arg Pro Gln Ala Ile Val Phe Glu Ile
1570 1575 1580

Val Thr Asp Lys Lys Phe Asp Ile Ile Ile Met Leu Phe Ile Gly Leu
1585 1590 1595 1600

Asn Met Phe Thr Met Thr Leu Asp Arg Tyr Asp Ala Ser Asp Thr Tyr
1605 1610 1615

Asn Ala Val Leu Asp Tyr Leu Asn Ala Ile Phe Val Val Ile Phe Ser
1620 1625 1630

Ser Glu Cys Leu Leu Lys Ile Phe Ala Leu Arg Tyr His Tyr Phe Ile
1635 1640 1645

Glu Pro Trp Asn Leu Phe Asp Val Val Val Val Ile Leu Ser Ile Leu
1650 1655 1660

Gly Leu Val Leu Ser Asp Ile Ile Glu Lys Tyr Phe Val Ser Pro Thr
1665 1670 1675 1680

Leu Leu Arg Val Val Arg Val Ala Lys Val Gly Arg Val Leu Arg Leu

1685 1690 1695

Val Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Ala Met
1700 1705 1710

Ser Leu Pro Ala Leu Phe Asn Ile Cys Leu Leu Leu Phe Leu Val Met
1715 1720 1725

Phe Ile Phe Ala Ile Phe Gly Met Ser Phe Phe Met His Val Lys Glu
1730 1735 1740

Lys Ser Gly Ile Asn Asp Val Tyr Asn Phe Lys Thr Phe Gly Gln Ser
1745 1750 1755 1760

Met Ile Leu Leu Phe Gln Met Ser Thr Ser Ala Gly Trp Asp Gly Val
1765 1770 1775

Leu Asp Ala Ile Ile Asn Glu Glu Ala Cys Asp Pro Pro Asp Asn Asp
1780 1785 1790

Lys Gly Tyr Pro Gly Asn Cys Gly Ser Ala Thr Val Gly Ile Thr Phe
1795 1800 1805

Leu Leu Ser Tyr Leu Val Ile Ser Phe Leu Ile Val Ile Asn Met Tyr
1810 1815 1820

Ile Ala Val Ile Leu Glu Asn Tyr Ser Gln Ala Thr Glu Asp Val Gln
1825 1830 1835 1840

Glu Gly Leu Thr Asp Asp Asp Tyr Asp Met Tyr Tyr Glu Ile Trp Gln
1845 1850 1855

Gln Phe Asp Pro Glu Gly Thr Gln Tyr Ile Arg Tyr Asp Gln Leu Ser
1860 1865 1870

Glu Phe Leu Asp Val Leu Glu Pro Pro Leu Gln Ile His Lys Pro Asn
1875 1880 1885

Lys Tyr Lys Ile Ile Ser Met Asp Ile Pro Ile Cys Arg Gly Asp Leu
1890 1895 1900

Met Tyr Cys Val Asp Ile Leu Asp Ala Leu Thr Lys Asp Phe Phe Ala
1905 1910 1915 1920

Arg Lys Gly Asn Pro Ile Glu Glu Thr Gly Glu Ile Gly Glu Ile Ala
1925 1930 1935

Ala Arg Pro Asp Thr Glu Gly Tyr Glu Pro Val Ser Ser Thr Leu Trp

1940 1945 1950

Arg Gln Arg Glu Glu Tyr Cys Ala Arg Leu Ile Gln His Ala Trp Arg
1955 1960 1965

Lys His Lys Ala Arg Gly Glu Gly Gly Gly Ser Phe Glu Pro Asp Thr
1970 1975 1980

Asp His Gly Asp Gly Gly Asp Pro Asp Ala Gly Asp Pro Ala Pro Asp
1985 1990 1995 2000

Glu Ala Thr Asp Gly Asp Ala Pro Ala Gly Gly Asp Gly Ser Val Asn
2005 2010 2015

Gly Thr Ala Glu Gly Ala Ala Asp Ala Asp Glu Ser Asn Val Asn Ser
2020 2025 2030

Pro Gly Glu Asp Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
2035 2040 2045

Ala Ala Gly Thr Thr Thr Ala Gly Ser Pro Gly Ala Gly Ser Ala Gly
2050 2055 2060

Arg Gln Thr Ala Val Leu Val Glu Ser Asp Gly Phe Val Thr Lys Asn
2065 2070 2075 2080

Gly His Lys Val Val Ile His Ser Arg Ser Pro Ser Ile Thr Ser Arg
2085 2090 2095

Thr Ala Asp Val
2100